The Versatility of α-Chloropropargyl Phenyl Sulfide Affords High Stereo- and Regioselectivities in Indium-Promoted Coupling Reactions under Mild Conditions

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Received July 31, 2001

Coupling reactions between α-chloropropargyl phenyl sulfide (**11**) and a series of aldehydes under aqueous conditions are reported. Not only is good stereoselectivity observed between syn and anti isomeric products, but excellent regioselectivity is also witnessed. In reactions using indium metal as a promoter, the propargyl functionality (**12**) is retained, unlike the use of more traditional metals that result in formation of products containing a mixture of both propargyl (**12**) and allene (**13**) moieties. The reaction is postulated to proceed via either a chelated or nonchelated route, controlled by the presence or absence of indium (III) chloride, and may be used to create synthetically useful building blocks. The formation of epoxyalkyne (**14**) molecules, which are found in many natural products and have wide use as synthetic templates, is presented as one example.

Introduction

The past decade has been witness to a large movement toward environmentally benign chemistry and chemical transformations. Chemists have sought to introduce more mild catalysts, reagents, and solvent systems into their work.[1] Indium metal has found much success in this area as it has been shown to promote the formation of C−C bonds under aqueous conditions with high yields and good control.[1,2] Indium metal has also been shown to possess good chelating properties under aqueous conditions, allowing for good stereo- and regioselectivities to be realized.[2,3] Many of the past studies utilizing this metal have focused on controlling ratios of syn/anti product formation in Barbier-type reactions by placing heteroatomic functional groups α or β to a carbonyl functionality.[3a,c,e] These systems have allowed control of product formation with diastereomeric ratios as high as 13:1.[3e] Placement of a heteroatomic group α or β to a carbonyl moiety is often not trivial, however, and may require multiple steps, making isolation and purification an arduous process.

One alternative to having the electrophilic component command the stereochemical outcome of reactions would be to have spatial relationships of newly forming stereocenters controlled by the nucleophile. One such set of nucleophiles that could be utilized in this sense would be α-chloroheteroatomic species, as shown in Scheme 1.[4]

α-Chloroheteroatomic species were implemented for use as early as the 1960s when Normant published a study of α-chlorosulfide reactivity.[5] He noted their effectiveness under Barbier- and Grignard-type conditions in C−C bond-forming reactions in these investigations.[5] Since then, other authors have used similar systems with varying degrees of success.[6] The chloride species in Scheme 1 are interesting for a variety of reasons: (1) Although not cited often in recent literature, their successful use in Barbier-type chemistry is quite intriguing. (2) The nucleophile contains a stereocenter that may be used to help control spatial alignments in product formation, eliminating the need to synthesize such a center α to the carbonyl in an electrophilic species. (3) Many compounds of the type shown in Scheme 1 are available in one step from easily obtainable starting materials, removing synthetic hurdles and simplifying the overall synthetic process.

In an effort to further studies in environmentally benign chemistry and chemical transformations, as well as to simplify and offer an alternative to known indium-promoted chemistry,[1] we decided to study α-chloro heteroatomic compounds for use as the nucleophilic components in indium-promoted reactions under aqueous conditions. This study focuses on stereo- and regiocontrol of product formation within these parameters with an

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[1] (a) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley and Sons: New York, 1997; Chapter 4. (c) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (d) Chan, T.-H.; Li, C.-J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, 1181. (e) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500. (f) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920. (g) Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 1378.

[2] For some recent examples of In-mediated reactions, refer to: (a) Lu, W.; Chan, T. H. *J. Org. Chem.* **2001**, *66*, 3467−3473. (b) Li, C.-J.; Li, J. *Tetrahedron Lett.* **2001**, *42*, 793. (c) Lee, P. H.; Ahn, H.; Lee, K.; Sung, S.-Y.; Kim, S. *Tetrahedron Lett.* **2001**, *42*, 37. (d) Paquette, L. A.; Rothhaar, R. R.; Isaac, M.; Rogers, L. M.; Rogers, R. D. *J. Org. Chem.* **1998**, *63*, 5463. (e) Loh, T.-P.; Zhou, J. R. *Tetrahedron Lett.* **1999**, *40*, 9115.

[3] (a) Paquette, L. A.; Lobben, P. C. *J. Org. Chem.* **1998**, *63*, 6990. (b) Paquette, L. A.; Bennett, G. D.; Chatriwalla, A.; Isaac, M. B. *J. Org. Chem.* **1997**, *62*, 3370 (c) Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917, (d) Paquette, L. A.; Mitzel, *J. Org. Chem.* **1996**, *61*, 8799. (e) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931.

[4] For nice reviews in this area: (a) Dilworth, B. M.; McKervey, M. A. *Tetrahedron* **1986**, *42*, 3731. (b) Peterson, D. J. *Organomet. Chem. Rev. A* **1972**, 295 and references cited therein.

[5] (a) Normant, H.; Castro, C. R. *Acad. Sci. Paris* **1964**, *259*, 830

[6] (a) Nakatsuka, S.; Takai, K.; Utimata, K. *J. Org. Chem.* **1986**, *51*, 5045. (b) Gross, H.; Hoft, E. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 335. (c) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1985**, *106*, 6902.

10.1021/jo015992l CCC: $22.00

Scheme 1

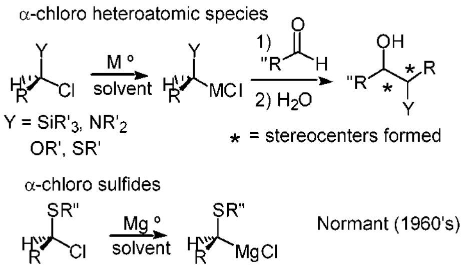
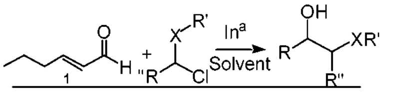
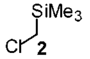
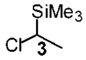
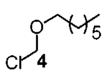
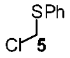


Table 1. Initial Coupling Reactions Using α-Chloroheteroatomic Reagents[10]



Entry	Halide	Solvent	Yield
1		H_2O	NR
2		DMF	65 %
3		H_2O	NR
4		DMF	66%
5		H_2O	59 %
6		H_2O/DMF	75 %
7		DMF^b	86 %
8		H_2O	86 %
9		H_2O/DMF	88 %
10		DMF^b	88 %

[a] Reactions were run at room temperature for a period of 1−20 h. Ratio of reagents was as follows: 1.0:1.5:1.1 (aldehyde/halide/Indium). The reaction was run at 0.1 M with respect to the amount of In. [b] Reactions run in DMF alone as a solvent required premixing of the chloride and indium metal with heating to 50 °C for 1 h for successful completion to occur.

emphasis toward the synthesis of epoxyalkyne[7−9] functional groups.

Results and Discussion

Early Studies. Early studies focused on determining the feasibility of indium-promoted C−C bond-forming reactions with α-chloroheteroatomic reagents and involved silyl, thio, and oxy species as summarized in Table 1.[10] As shown with entries 1−4 in Table 1, use of silyl chlorides did not auger well in these studies. This is most likely due to the lability of silicon under aqueous conditions, destroying the nucleophilic reagent before reaction occurs. As entries 2 and 4 of Table 1 reveal, switching from H_2O to DMF allows the reaction to proceed; however, yields are moderate at best. Use of α-chlorooxy species proceeded more smoothly; however, loss of the nucleophile was still problematic within these parameters. Following the reaction by thin-layer chromatography (TLC 10:1 hexanes/ethyl acetate) shows a smooth beginning to the reaction sequence. As the reaction progresses, however, the nucleophile disappears, while the aldehyde concentration remains unchanged. Addition of DMF promotes a consistent rate of disappearance for both the aldehyde and nucleophile while increasing overall yields (entries 5−7, Table 1). Previous studies have indicated that indium-promoted couplings become more acidic as the reaction proceeds.[3] This trend was also seen in the present case and is believed to be the cause of nucleophilic destruction of the α-chlorooxy species during reaction under solely aqueous conditions. Admixing DMF into the aqueous solvent or replacement of water with DMF stabilizes the pH during reaction, slowing destruction of the nucleophilic species. Entries 8−10 (Table 1) show that greatest consistency is realized when α-chlorosulfide species are used to form the nucleophilic species in these C−C bond-forming reactions. The sulfide species studied during this phase of work gave high yields under a plethora of conditions and ran more cleanly than when other chlorides were used, simplifying isolation of products. Although all systems tested had shown success under the conditions implemented, due to superior yields and easier isolation of products, it was decided to focus on the sulfur species.[10]

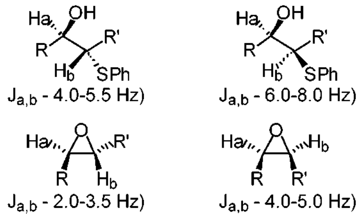


Figure 1. Representative *J* values for hydroxy sulfides and epoxides.

Stereoselective Studies with α-Chlorosulfides. The next phase of our study focused on determining whether the chlorosulfide compounds could form products exhibiting stereocontrol. Diastereomeric products were distinguished either by direct determination of vicinal coupling constants in the hydroxy sulfides where possible or by conversion to epoxide compounds (Figure 1).[11]

Table 2 summarizes work completed on stereoselectivity investigations, revealing the overall diastereoselective control realized using a variety of α-chlorosulfides and aldehydes. Entries 1−4 (Table 2), which used hexenal as the electrophile, seemed to fare more poorly with respect to both yield and stereoselectivity. Product ratios using this aldehyde were approximately 1:1 with isolated yields in the range of 65−70%. Other systems were more successful with ratios as high as 88:12 (entry 23, Table 2) seen for syn selectivity and 80:20 (entries 7, 18, and 21, Table 2) for anti selectivity. As noted in Table 2, reactions run in the absence of $InCl_3$ resulted in predominant formation of the anti diastereomer, while

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[7] (a) Kanger, T.; Piret, J.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Tetrahedron*: *Asymmetry* **1998**, *9*, 2499. (b) Bohlmann, F.; Burkhardt, T.; Zdero, C. *Naturally Occurring Acetylenes*: Academic Press: New York, 1973.

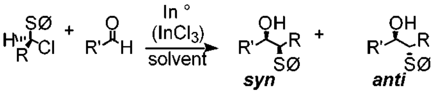
[8] (a) For a nice review of this material: Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 9369. (c) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466 and references therein.

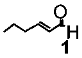
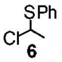
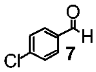
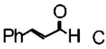
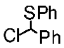
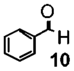
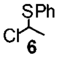
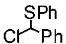
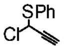
[9] (a) König, B.; Pitsch, W.; Klein, M.; Vasold, R.; Prall, M.; Schreiner, P. R. *J. Org. Chem.* **2001**, *66*, 1742. (b) Wang, G. X.; Iguchi, S.; Hirama, M. *J. Org. Chem.* **2001**, *66*, 2146. (c) Gebauer, O.; Brückner, R. *Synthesis* **2000**, 588. (d) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2732.

[10] Engstrom, G.; Morelli, M.; Palomo, C.; Mitzel, T. *Tetrahedron Lett.* **1999**, *40*, 5967.

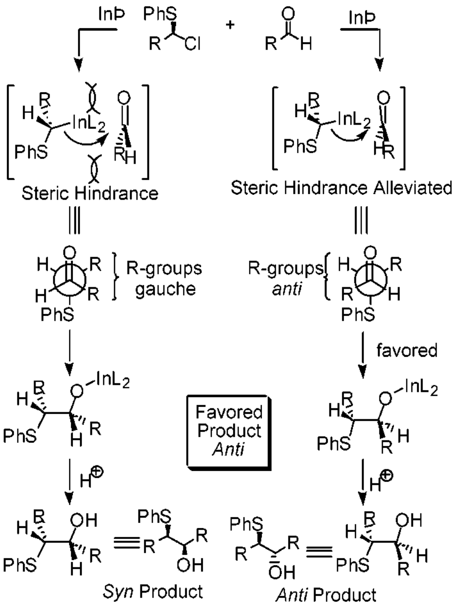
[11] (a) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. M. *J. Org. Chem.* **1997**, *62*, 4293. (b) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 6116. (c) Shimagaki, M.; Maeda, T.; Matsuzaki, Y.; Hori, I.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, *25*, 4775.

Table 2. Initial Stereoselectivity Studies



	Aldehyde	Halide	Solvent	Ratio (*syn*:*anti*)	Yield
1	 **1**	 **6**	H_2O	40:60	65%
2			DMF	58:42	70%
3			$H_2O/InCl_3$	54:46	65%
4			DMF/$InCl_3$	61:39	70%
5	 **7**		DMF	26:74	~70%
6			DMF:$H_2O/InCl_3$	80:20	75-80%
7			H_2O	20:80	79%
8			$H_2O/InCl_3$	85:15	74%
9	 **8**	 **9**	THF	50:50	60-65%
10			THF/$InCl_3$	50:50	50%
11			H_2O	22:78	70-75%
12	 **10**	 **6**	H_2O	25:75	84%
13			DMF/H_2O	29:71	73%
14			$H_2O/InCl_3$	77:23	87%
15			DMF/$H_2O/InCl_3$	78:22	81%
16		 **9**	DMF	37:63	~70%
17			DMF:$H_2O/InCl_3$	80:20	75-80%
18			H_2O	20:80	79%
19			$H_2O/InCl_3$	86:14	74%
20		 **11**	H_2O	30:70	70%
21			DMF/H_2O	**20:80**	83%
22			$H_2O/InCl_3$	78:22	87%
23			H_2O/DMF/$InCl_3$	**88:12**	84%

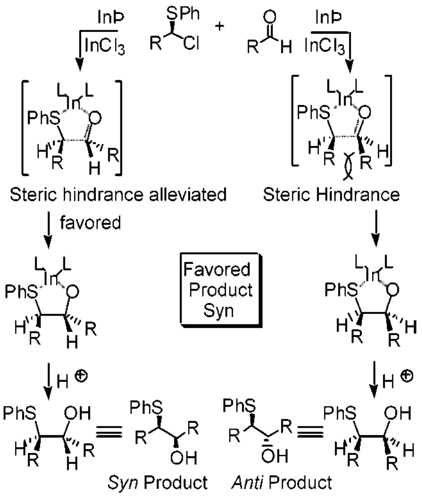
Scheme 2



reactions run in the presence of $InCl_3$ resulted in predominant formation of the syn isomer. The reaction is postulated to proceed via two possible pathways, a nonchelated route (Scheme 2) and a chelated route (Scheme 3).[10]

A nonchelated pathway has two possible tracks, as shown in Scheme 2. In each of the two possible routes, the heteroatoms will approach each other in an anti fashion. Following this scheme along the left-hand route, we can see that the two R groups will be situated gauche to each other. Steric hindrance encountered along this route will raise the energy sufficiently to favor the right-hand track of a nonchelated pathway. In the absence of $InCl_3$, it is presumed that this pathway is favored, giving rise to predominantly anti product formation in our systems.

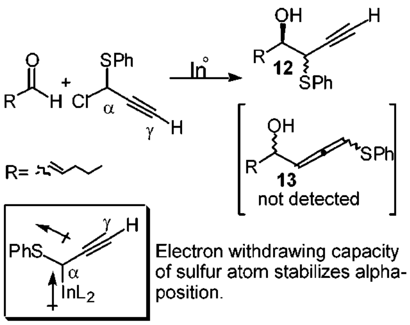
Scheme 3



When $InCl_3$ is added to the reaction mixture, syn product formation predominates. It is postulated that, with the presence of $InCl_3$, a chelated pathway is followed as shown in Scheme 3. Indium trichloride ($InCl_3$) chelates to the sulfur and oxygen heteroatoms, giving a five-membered ring intermediate. The R groups on each of our two species may approach from either the same side as shown on the right-hand track of Scheme 3 or from the opposite sides as shown from the left-hand track of Scheme 3. Steric hindrance encountered along the right-hand pathway of this chelated route will raise the overall energy sufficiently to favor the left-hand track. Following the left-hand track leads to syn product formation, which is what is witnessed when $InCl_3$ is added to our reaction mixtures. In previous work, Whitesides and others have shown that it is possible to carry out reactions under aqueous conditions with preformed allymetal reagents,[1e−g] lending credence to Schemes 2 and 3. Chan and Li have proposed a SET reaction on the metal surface,[1a−d] which also has good merit and would still not discount a general scheme such as shown above. While the precise mechanism remains allusive, it has been suggested that it may be a combination of SET and organometallic species[1b] and that alteration of reaction conditions or reagents could modify the pathway to some extent.

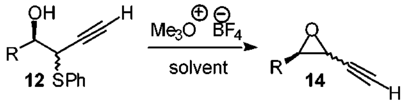
Entries 20−23 (Table 2) are interesting for a couple of reasons. Not only are syn/anti ratios highest for this set of entries of our study, but the chloride species used in this system has a propargyl group integrated into its skeletal structure. It was noted that the propargyl group of the nucleophile was retained in this reaction (Scheme 4),[12] which is interesting as there are few examples of retention of the alkyne group when propargylic nucleophiles with terminal alkynes are used in coupling reactions.[12b,e] Often, the final product is an allene or a mixture of allene and alkyne moieties.[12] We detected no allene and surmise that the σ electron-withdrawing

Scheme 4



capacity of sulfur stablizes the α-position, allowing for attack to originate from this position in preference over the γ- site.

Exposure of **12** to trimethyloxonium tetrafluoroborate[13] leads to formation of an epoxy alkyne (**14**) in reasonable to good yields (eq 1).[10]



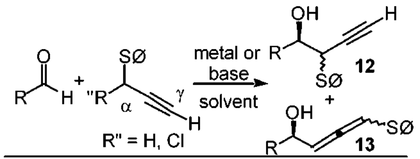
(1)

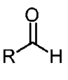
This interesting result deserved further scrutiny and induced investigation toward the next phase of this study.

Stereo- and Regioselectivity Studies with Propargyl Sulfides. Stereoselective formation of epoxy alkynes (**14**) has emerged as an area of increasing interest in recent years due to their unique skeletal design and use in formation of more complicated structural systems.[14,15] Procedures applied in formation of epoxy alkynes such as use of *m*-CPBA[16] and oxone[17] and ring closure of halohydrin precursors have been successful, but only a limited number of examples are found in the literature.[18] An indium-based methodology using propargyl sulfides such as shown in entries 20–23 (Table 2) would offer a nice addition in this area of chemistry.[14–18]

Our interest was piqued as to whether the alkyne (**12**) was retained solely due to effects of sulfur or whether the metal contributed to this regioselectivity as well. With this in mind, our first area of focus centered on the ratio of **12** to **13** formed using traditional methods, which have historically relied upon lithium, magnesium, or copper intermediates to ensure successful transformation.[1,15]

Table 3. Coupling Reactions Using "Traditional" Methods



entry	aldehyde	metal/solvent	ratio 12:13
1		Mg °/ THF	NR
2		Rieke Mg °/ THF or DMF	~1.3 : 1.0
3		Rieke Mg °/CuCl/ THF	~1.0 : 1.7
4		n-BuLi / THF	~1.3 : 1.0
5		EtMgBr / THF	~1.3 : 1.0

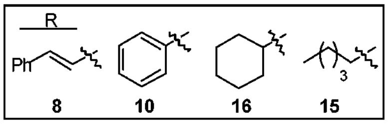


Table 3 presents the results obtained when magnesium, copper, and lithium intermediates are utilized. With respect to those reactions in which a Grignard reagent was formed, α-chloropropargylphenyl sulfide (**11**) was added to a THF or DMF solution containing magnesium metal. This mixture was stirred for a period of 1–3 h with heating, at which time the aldehyde was added. Entries 1–3 (Table 3) reveal the necessity of having to activate the magnesium under Rieke conditions[19] for this reaction to proceed in a satisfactory manner. It was also necessary to add the aldehyde slowly, over 6–8 h, with a syringe pump. If the aldehyde was added too quickly, decomposition of starting materials was noted, with no discernible amount of product isolation attained. In each of the procedures where magnesium metal was used to promote coupling, a mixture of alkyne (**12**) and allene (**13**) was isolated with very little preference observed for either species. During several trials, CuCl was added to the Grignard reagent, facilitating formation of a copper intermediate. Products isolated under these conditions were similar to those displayed when magnesium metal was the sole component, although allene (**13**) to alkyne (**12**) ratios were slightly increased. Deprotonation of propargyl phenyl sulfide en route to epoxy alkyne formation was also undertaken. Propargyl phenyl sulfide was dissolved in THF and the solution cooled to 0 °C, at which time base was added via syringe pump over 3 h. Adding the base more quickly led to decomposition of the sulfide. After addition was complete, the solution was warmed to room temperature and the aldehyde admixed over 6–8 h. Yields obtained following this technique were in the 70–80% range; however, as was evidenced with earlier Grignard and copper reagent studies, little selectivity between **12** and **13** was noted.

The next step in this study was to couple α-chloropropargyl sulfide with various aldehydes using indium metal as a promoter, allowing a direct comparison of this new methodology with the more traditional coupling techniques. Results garnered under these conditions are shown in Table 4.

Not only was excellent regioselectivity observed but good stereocontrol was also exhibited when coupling

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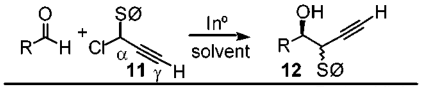
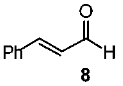
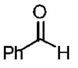
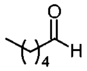
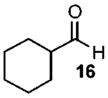
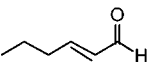
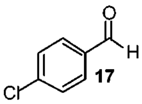
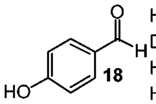
Table 4. Indium-Promoted Coupling Reactions Using α-Chloropropargyl Phenyl Sulfide[a]



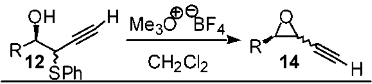
entry	R	Solvent	Ratio syn:anti	Yield (%)
1	 **8**	H_2O	40:60	68
2		DMF/H_2O	**26:74**	73
3		H_2O/$InCl_3$	68:32	69
4		H_2O/DMF/$InCl_3$	**90:10**	75
5	 **10**	H_2O	30:70	70[10]
6		DMF/H_2O	**20:80**	83
7		H_2O/$InCl_3$	78: 22	87[10]
8		H_2O/DMF/$InCl_3$	**88:12**	84
9	 **15**	H_2O	**45:55**	47
10		DMF/H_2O	**45:55**	56
11		H_2O/$InCl_3$	51:49	48
12		H_2O/DMF/$InCl_3$	**53:47**	46
13	 **16**	H_2O	40:60	80
14		DMF/H_2O	**33:67**	87
15		H_2O/$InCl_3$	71:29	78
16		H_2O/DMF/$InCl_3$	**87:13**	77
17	 **1**	H_2O	34:66	68[10]
18		DMF/H_2O	**32:68**	68
19		H_2O/$InCl_3$	**77:23**	83[10]
20		H_2O/DMF/$InCl_3$	76:24	84
21	 **17**	H_2O	**33:67**	82
22		DMF/H_2O	35:65	77
23		H_2O/$InCl_3$	**66:33**	74
24		H_2O/DMF/$InCl_3$	63:37	80
25	 **18**	H_2O	30:70	86
26		DMF/H_2O	**16:84**	87
27		H_2O/$InCl_3$	68:32	72
28		H_2O/DMF/$InCl_3$	**83:17**	74

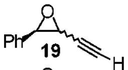
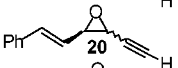
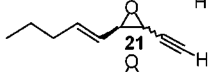
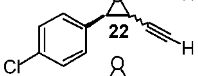
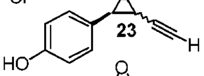
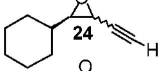
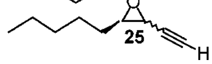
[a] Reactions were run at room temperature for a period of 1−30 h. The ratio of reagents was as follows: 1.0:1.5:1.1 (aldehyde/halide/indium). The reaction was run at 0.1 M with respect to the amount of In.

aldehydes with α-chloropropargyl sulfide using indium metal as the promoter. Again, the two diastereomeric products were distinguished either by direct determination of vicinal coupling constants in the hydroxy sulfides where possible or by conversion to the corresponding epoxides (Figure 1).[11] As noted by entries **2**, **6**, **18**, and **26** (Table 4), superior anti ratios were obtained in solvent mixtures containing equal amounts of water and DMF. Once again, addition of $InCl_3$ to our aldehyde and α-chloroalkyl phenyl sulfide mixtures favored formation of syn isomers. As was seen with reactions run in the absence of $InCl_3$, solvent mixtures containing an equal amount of water and DMF afforded the highest ratios of syn to anti products when $InCl_3$ was present. Attempts to run reactions in DMF alone required premixing of the indium and α-chloro sulfide species with heating to 50 °C for 1 h. After this time, the mixture was cooled and aldehyde added. Product selectivities under these conditions were not improved, and yields tended to average under 50%. As a result, this pathway was not scrutinized further.

Systems listed in Table 4 were converted to epoxy alkyne moieties by treatment of the hydroxy sulfide with a solution of trimethyloxonium tetrafluoroborate[13a] or TlOEt,[13b] resulting in formation of the desired epoxyalkyne (Table 5).

Table 5. Conversion of Hydroxy Sulfides to Epoxy Alkynes



	hydroxysulfide mixture (Table 4 entry)	epoxyalkyne	Ratio syn:anti
1	**6**	 **19**	20:80
2	**8**		88:12
3	**2**	 **20**	26:74
4	**4**		90:10
5	**18**	 **21**	32:68
6	**20**		77:23
7	**21**	 **22**	33:66
8	**23**		66:33
9	**26**	 **23**	16:84
10	**28**		83:17
11	**10**	 **24**	33 67
12	**12**		87:13
13	**13**	 **25**	45:55
14	**16**		53:47

As seen in Table 5, successful formation of the epoxy alkyne was evidenced with each system. Yields of conversion ranged from 65 to 75% with no loss of syn/anti ratios with respect to the beginning hydroxy sulfide compound noted. With entries **3/4**, **5/6**, and **13/14** of Table 5, some alkene product was detected. We were unable to isolate and confirm the structure of this contaminant species; however, overall conversions were quite successful, offering easy entry into synthetically useful epoxy alkyne molecules.

In conclusion, indium-promoted coupling of α-chloropropargyl phenyl sulfide with aldehyde functional groups proceeds with superior regioselectivity to historically traditional metal insertion or base conditions. Indium-promoted couplings of these systems also proceed with very good stereoselectivity, allowing easy entry into the formation of epoxy alkyne compounds, which have both natural[14] and synthetic[14,15] importance. Use of indium metal to promote these reactions offers mild, more environmentally benign conditions than traditional promoters and has also proven to be more efficient. This chemistry should open new pathways of study into this area and in indium-promoted coupling reactions as a whole. Further studies including the use of these species to form enediyne and epoxydiyne molecules are currently in progress.

Experimental Section

General Experimental Procedures. Tetrahydrofuran was purified by distillation under an argon atmosphere over sodium and benzophenone prior to use. Dimethylformamide and CCl_4 were purified by distillation over CaH_2 prior to use. All other solvents were used as purchased. All other reagents were used as purchased from Aldrich Chemical Co. Selecto Scientific 63-200 particle size silica gel was used for column chromatography. Radial chromatography was performed using a Chromatatron purchased from Harrison Research.

A. General Experimental Procedure for Coupling Reactions Performed in Water as a Solvent with Indium Metal as a Promoter. A magnetically stirred solution of aldehyde (1.0 mmol) in 11 mL of deionized water was treated with α-chloroalkyl phenyl sulfide (1.5 mmol) and indium powder (127 mg, 1.10 mmol). The solution was allowed to proceed at room temperature until no aldehyde was detected by TLC analysis. Dichloromethane (20 mL) was added, and stirring was maintained for 30 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried and evaporated to leave a light yellow oil. Purification was accomplished by flash chromatography on silica gel (elution hexanes−ethyl acetate) or by radial chromatography where possible. In some cases, the hydroxy sulfide mixtures were analyzed without further separation.

B. General Experimental Procedure for Coupling Reactions Performed in Water/Dimethylformamide Mixtures with Indium Metal as a Promoter. A magnetically stirred solution of aldehyde (1.0 mmol) in a 50:50 mixture of deionized water and dimethylformamide (11 mL) was treated with α-chloroalkyl phenyl sulfide (1.5 mmol) and indium powder (127 1.1 mmol). The solution was allowed to proceed at room temperature until no aldehyde was seen (TLC analysis). Dichloromethane (20 mL) was added, and stirring was maintained for 30 min. The layers were separated and the aqueous phase extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried and evaporated to leave a brown oil that was separated by silica gel (elution hexanes−ethyl acetate) or by radial chromatography where possible. In some cases, the hydroxy sulfide mixtures were analyzed without further separation.

C. Coupling Procedures Used during Initial Stereoselectivity Studies. I. Coupling Reaction between 2-Hexenal (1) and α-Chloroethyl Phenyl Sulfide (6). The general procedure was followed as described in A. Purification was accomplished by flash chromatography on silica gel (elution 150:1 hexanes−ethyl acetate) to give a mixture of hydroxy sulfides as a light yellow oil. Yield = 154 mg (0.65 mmol) = 65%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.94−2.02 (m, 7H), 1.28 (d, 1.8H, $J = 6.0$ Hz), 1.32 (d, 1.2H, $J = 6.0$ Hz), 2.82 (m, 1H), 4.05 (dd, 0.4H, $J = 7.1$, 2.7 Hz), 4.17 (dd, 0.6H, $J = 4.5$, 2.7 Hz), 5.41 (m, 1H), 5.69 (m, 1H), 7.03−7.16 (m, 5H), OH proton was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ: (14.1, 14.6), 16.2, 24.0, 33.1, (47.7, 48.1), (81.1, 82.0), 125.0, 126.3 (2), 128.3, 128.4, 128.5, 128.7, 137.1. MS m/z: (M^+) calcd 236.1235, obsd 236.1291. Anal. Calcd for $C_{14}H_{20}OS$: C, 71.14; H, 8.53. Found: C, 71.17; H, 8.48.

II. Coupling Reaction between *p*-Chlorobenzaldehyde (7) and α-Chloroethyl Phenyl Sulfide (6). The general procedure was followed as described in A. Purification was accomplished by flash chromatography on silica gel (elution 50:1 hexanes−ethyl acetate) to give a mixture of hydroxy sulfides as a light yellow oil. Yield = 440 mg (1.58 mmol) = 79%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.32 (d, 2.4H, $J = 5.8$ Hz), 1.36 (d, 0.6H, $J = 5.8$ Hz), 3.11 (m, 1H), 4.59 (d, 0.2H, $J = 7.3$ Hz), 4.64 (d, 0.8H, $J = 4.7$ Hz), 7.02−7.20 (m, 9H), OH proton was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ: (14.4, 14.9), (48.5, 49.1), 81.7, 124.3, (126.4, 126.6), 126.8, 128.4 (2), 129.0 (2), 129.7, 129.9, (132.4, 132.7). MS m/z: (M^+) calcd 278.0532, obsd 278.0551. Anal. Calcd for $C_{15}H_{15}ClOS$: C, 64.62; H, 5.42. Found: C, 64.83; H, 5.65.

III. Coupling Reaction between Cinnamaldehyde (8) and α-Chlorobenzyl Phenyl Sulfide (9). The general procedure was followed as described in A. Separation of diastereomers was obtained by radial chromatography (elution with 100:1 hexanes−ethyl acetate) to give the hydroxy sulfides as light yellow oils. Yield = 485 mg (1.46 mmol) = 73%.

Syn Isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.93 (d, 1H, $J = 7.9$ Hz), 4.51 (m, 1H), 6.19 (m, 1H), 6.57 (d, 1H, $J = 2.8$ Hz), 6.99−7.21 (m, 15H), OH proton was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.9, 80.1, 125.0, 126.1, 126.2 (2), 126.4 (2), 126.9, 127.3, 127.5, 127.7 (2), 128.2, 128.3, 128.4 (2), 128.7 (2), 133.1, 135.1, 142.3. MS m/z: (M^+) calcd 332.1235, obsd 332.1241. Anal. Calcd For $C_{22}H_{20}OS$: C, 79.48; H, 6.06. Found: C, 79.21; H, 6.11.

Anti Isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.01 (d, 1H, $J = 4.9$ Hz), 4.55 (m, 1H0, 6.05 (m, 1H), 6.52 (d, 1H, $J = 2.7$ Hz), 6.99−7.24 (m, 15H), OH proton was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.5, 80.1, 125.4, 125.9, 126.1, 126.4 (3), 126.9, 127.3, 127.7 (3), 128.2 (2), 128.4 (2), 128.7 (2), 129.8, 135.2, 142.3. MS m/z: (M^+) calcd 332.1235, obsd 332.1229. Anal. Calcd for $C_{22}H_{20}OS$: C, 79.48; H, 6.06. Found: C, 79.71; H, 6.14.

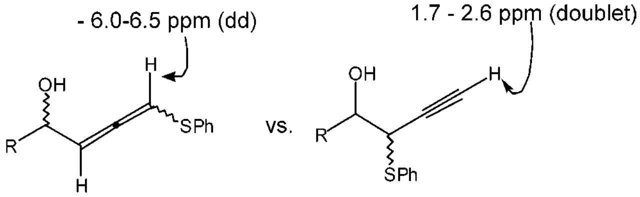
IV. Coupling Reaction between Benzaldehyde (10) and α-Chloroethyl Phenyl Sulfide (6). The general procedure was followed as described in A. Purification was accomplished by radial chromatography on silica gel (elution 100:1 hexanes−ethyl acetate) to give a mixture of hydroxy sulfides as a colorless oil. Yield = 205 mg (0.84 mmol) = 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, 0.75 H, $J = 6.1$ Hz), 1.33 (d, 2.25H, $J = 6.1$ Hz), 3.10 (m, 1H), 4.69 (d, 0.25H, $J = 7.9$ Hz), 4.81 (d, 0.75H, $J = 4.1$ Hz, 7.00−7.18 (m, 10H), OH proton was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ: (15.0, 16.1), (47.9, 48.5), (81.6, 82.0), 124.3, 125.8, 126.7 (2), 128.1, 128.3, 128.7 (2), 129.0 (2), (135.4, 135.9), (138.9, 140.4); MS m/z: (M^+) calcd 244.0922, obsd 244.0917. Anal. Calcd for $C_{15}H_{16}OS$: C, 73.73; H, 6.60. Found: C, 73.65; H, 6.67.

V. Coupling Reaction between Benzaldehyde (10) and α-Chlorobenzyl Phenyl Sulfide (9). The general procedure was followed as described in A. Separation of diastereomers was obtained by radial chromatography (elution with 50:1 hexanes−ethyl acetate) to give the hydroxy sulfides as light yellow oils. Yield = 425 mg (1.39 mmol) = 70%.

Syn Isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.21 (d, 1H, $J = 7.7$ Hz), 5.09 (d, 1H, $J = 7.7$ Hz), 7.01−7.16 (m 15H), OH proton was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 54.8, 81.5, 124.4, 125.9, 126.0, 126.2, 126.9, 127.2, 127.4, 127.6 (2), 128.3 (2), 128.6 (3), 128.7, 135.2, 140.8, 141.3. MS m/z: (M^+) calcd 306.1078, obsd 306.1069. Anal. Calcd for $C_{20}H_{18}OS$: C, 78.39; H, 5.92. Found: C, 78.51; H, 6.01.

Anti Isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.37 (d, 1H, $J = 4.1$ Hz), 5.27 (d, 1H, $J = 4.1$ Hz), 7.00−7.16 (m, 15H), OH proton was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 52.5, 80.6, 125.6, 125.6, 125.9, 126.4 (3), 126.9, 127.3, 127.7 (3), 128.2 (2), 128.4 (2), 128.7 (2), 130.1, 135.2, 143.9. MS m/z: (M^+) calcd 332.1235, obsd 332.1248. Anal. Calcd for $C_{20}H_{18}OS$: C, 78.39; H, 5.92. Found: C, 78.99; H, 6.10.

D. Coupling Reactions Using the Propargyl Phenyl Sulfide Reagent. I. Coupling Procedures between Aldehydes and α-Chloropropargyl Phenyl Sulfide (11) Using Magnesium and Copper Intermediates To Form Hydroxy Sulfide Molecules. A. Coupling of Benzaldehyde (10) with α-Chloropropargyl Phenyl Sulfide (11) Using Magnesium Metal under Rieke Conditions. The activated magnesium was prepared by in situ reduction of magnesium chloride with lithium naphthalenide using a procedure by Rieke,[12a] Watanabe,[12b] and Arnold.[12c] To a solution of 50 mL of tetrahydrofuran in a flanged 100 mL three-necked flask equipped with an argon inlet and a Teflon-coated stirring bar were added naphthalene (1.232 g, 9.6 mmol) and approximately 2.0 g of sand. The solution was stirred at a vigorous rate, and lithium metal (66 mg, 9.6 mmol), which had been pounded flat under mineral oil and cut into strips, was added over 2 min. The mixture was stirred until a green color predominated and lithium metal was no longer detected. After formation of the lithium naphthalenide was complete, magnesium chloride (450 mg, 4.8 mmol) was added to the solution all at once. The suspension was stirred for 90 min, at which time α-chloropropargyl phenyl sulfide (**11**) (870 mg, 4.8 mmol) was added. The suspension was stirred for 2.5 h, and benzaldehyde (535 mg, 5.0 mmol), dissolved in 10 mL of tetrahydrofuran, was added to the flask via syringe over 2.5 h. The solution was stirred for 5 h at which time no **10** was seen (TLC analysis). The solution was transferred to a 500 mL flask, and 100 mL of dichloromethane along with 100 mL of hydrochloric acid (3 M solution) were added. Stirring was continued for an additional 45 min. The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with a sodium bicarbonate solution (saturated, 2 × 20 mL) and water (2 × 20 mL), dried, and evaporated to leave a light yellow oil. The products were analyzed by ^{1}H NMR with no further purification.



Mixture ratios, in general, between allene and alkyne products were determined by comparing the allene proton shift, which is approximately δ 6.0−6.5 ppm, and the terminal proton of the alkyne moiety, which occurs between δ 1.7 and 2.6 ppm depending on the nature of R.

B. Coupling of Benzaldehyde (10) with α-Chloropropargyl Phenyl Sulfide (11) Using a Copper Intermediate. The same procedure as described for coupling procedures using magnesium metal were used with the following change:

After formation of the Grignard reagent was complete, copper(I) chloride (475 mg, 4.8 mmol) was added with stirring for 60 min. The aldehyde was added in the usual manner, with workup as described above to leave a light yellow oil. The products were analyzed by ^{1}H NMR with no further purification in the manner described in section I. A. above.

C. Coupling of Aldehydes 8, 15, and 16 with α-Chloropropargyl Phenyl Sulfide (11) Using Magnesium Metal under Rieke Conditions. Processing and analysis of these reactions proceeded in the manner described above in section I. A.

Coupling of Aldehydes 8, 15, and 16 with α-Chloropropargyl Phenyl Sulfide (11) Using a Copper Intermediate. Processing and analysis of these reactions proceeded in the manner described above in section I. B.

II. Coupling Procedures for Phenylpropargyl Sulfide under Basic Conditions. A. Coupling of Cinnamaldehyde (8) with Phenylpropargyl Sulfide under Basic Conditions Using *n*-Butyllithium. Propargyl phenyl sulfide (604 mg, 4.0 mmol) was dissolved in 20 mL of tetrahydrofuran in a flame-dried 100 mL flask under a nitrogen atmosphere. The solution was cooled to 0 °C, and *n*-butyllithium (2 mL, 2 M solution) was added via syringe pump over 3 h. The solution was allowed to warm to room temperature. Cinnamaldehyde (527 mg, 4.0 mmol), dissolved in 10 mL of tetrahydrofuran, was added to the flask over 7 h via syring pump. The solution was stirred for an additional 1.5 h at which time no aldehyde was detected (TLC analysis). Dichloromethane (20 mL) and hydrochloric acid (3.0 M solution, 20 mL) were added with stirring for 40 min. The layers were separated and the aqueous layer extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with a sodium bicarbonate solution (saturated, 2 × 20 mL) and water (2 × 20 mL), dried, and evaporated to leave a light yellow oil. The products were analyzed by ^{1}H NMR with no further purification in the manner previously described for **10** in section I. A.

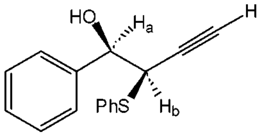
B. Coupling of Aldehydes 15 and 16 with Phenylpropargyl Sulfide under Basic Conditions Using *n*-Butyllithium. Processing and analysis of these reactions proceeded in the manner described above for **8** under basic conditions using *n*-butyllithium in section II. A.

C. Coupling of Cinnamaldehyde (8) with Phenylpropargyl Sulfide under Basic Conditions Using Ethylmagnesium Bromide. Propargyl phenyl sulfide (604 mg, 4.0 mmol) was dissolved in 20 mL of tetrahydrofuran in a flame-dried 100 mL flask under a nitrogen atmosphere. The solution was cooled to 0 °C, and ethylmagnesium bromide (2 mL, 2 M solution) was added via syringe pump over 3 h. The solution was allowed to warm to room temperature. Cinnamaldehyde (**8**) (527 mg, 4.0 mmol), dissolved in 10 mL of tetrahydrofuran, was added to the flask over 7 h via syring pump. The solution was stirred for an additional 2.5 h at which time no aldehyde was detected (TLC analysis). Dichloromethane (20 mL) and hydrochloric acid (3.0 M solution, 20 mL) were added with stirring for 40 min. The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with a sodium bicarbonate solution (saturated, 2 × 20 mL) and water (2 × 20 mL), dried, and evaporated to leave a light yellow oil. The products were analyzed by ^{1}H NMR with no further purification in the manner previously described for **10** in section I. A.

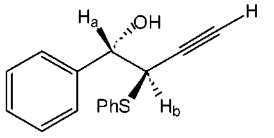
D. Coupling of Aldehydes 15 and 16 with Phenylpropargyl Sulfide under Basic Conditions Using Ethylmagnesium Bromide. Processing and analysis of these reactions proceeded in the manner described above for **8** under basic conditions using ethylmagnesium bromide in section II. C.

III. Coupling Procedures Using Indium Intermediates in Water as Solvent. A. Coupling of Benzaldehyde (10) with α-Chloropropargyl Phenyl Sulfide (11) Using Indium Metal in Water. The general procedure was followed as described in A. Purification was accomplished by flash chromatography on silica gel (elution with 40:1 hexanes−ethyl acetate) to give a mixture of hydroxy sulfides as a light yellow oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.77 (d, 1.6 Hz, 0.3H), 1.82 (d, J = 1.6 Hz, 0.7H), 4.05 (dd, J = 1.6, 8.1 Hz, 0.3H), 4.12 (dd, J = 1.6, 5.1, 0.7H), 4.71 (d, J = 8.1 Hz, 0.3H), 4.82 (d, J = 5.1 Hz, 0.7H), 7.19−7.02 (m, 10H) OH proton not detected. ^{13}C NMR (75 MHz, CDCl$_3$) δ: (44.9, 50.1), (67.1, 67.5), (77.5, 77.9), (85.5, 86.1), 125.5, 126.6 (2), 127.3, 127.4, 127.5, 128.7 (3), 128.8, 135.6 140.9. MS *m*/*z*: (M$^+$) calcd 254.0766, obsd 237.3447 (loss of H$_2$O, parent not observed). Anal. Calcd for C$_{16}$H$_{14}$OS: C, 75.55; H, 5.55. Found: C, 75.89; H, 5.61.



Hb : δ 4.05 ($J_{b,a}$ = 8.1 Hz)



Hb : δ 4.12 ($J_{b,a}$ = 5.1 Hz)

B. **Coupling of Aldehydes 1, 8, and 15−18 with α-Chloropropargyl Phenyl Sulfide (11) Using Indium Metal in Water.** Processing and analysis of these reactions proceeded, for the most part, in the manner described above for **10** in section III. Any deviations are listed below in the appropriate areas.

1. Analysis of Product Mixture Obtained from Coupling of 1 with α-Chloropropargyl Phenyl Sulfide (11). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.98−0.99 (m, 7H), 1.87 (d, J = 1.9 Hz, 0.34H), 1.90 (d, J = 1.9 Hz, 0.66H), 3.67 (dd, J = 1.9, 7.2 Hz, 0.34H), 3.73 (dd, J = 1.9, 4.2 Hz, 0.66H), 4.2 (m, 1H), 5.67 (m, 1H), 5.75 (m, 1H), 7.15−7.10 (m, 5H), OH proton was not detected. ^{13}C NMR (75 MHz, CDCl$_3$) δ: (14.5, 15.1), 23.4, (35.8, 36.1), 42.2, (67.8, 68.1), (85.3, 87.6), (71.7, 72.1), 123.2, 123.3, 125.0, 128.4 (2), 128.8, 129.3, 136.8. MS *m*/*z*: (M$^+$) calcd 246.1078, obsd 246.1061. Anal. Calcd for C$_{15}$H$_{19}$OS: C, 73.13; H, 7.36. Found: C, 74.00; H, 7.53.

2. Analysis of Product Mixture Obtained from Coupling of 8 with α-Chloropropargyl Phenyl Sulfide (11). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.87 (d, J = 2.1 Hz, 0.4H), 1.95 (d, J = 2.1 Hz, 0.6H), 3.58 (dd, J = 2.1, 7.6 Hz, 0.4H), 3.69 (dd, J = 2.1, 4.7 Hz, 0.6H), 4.2 (m, 1H), 6.25 (m, 1H), 6.62 (d, J = Hz, 1H), 7.30−7.08 (m, 10H) OH proton not detected. ^{13}C NMR (75 MHz, CDCl$_3$) δ: (42.8, 43.1), 65.5, 76.9, (87.1, 87.5), 125.1, 126.2, 126.3, 126.5, 126.7 (2), 127.3, 127.7, 128.6 (3), 128.9, 134.2, 136.0. MS *m*/*z*: (M$^+$) calcd 280.0922, obsd 280.0887. Anal. Calcd for C$_{18}$H$_{16}$OS: C, 77.11; H, 5.75. Found: C, 76.99; H, 5.61.

3. Analysis of Product Mixture Obtained from Coupling of 15 with α-Chloropropargyl Phenyl Sulfide (11). Separation proceeded in the same manner as described above; however, separation was not obtained, and the ^{1}H NMR was not conclusive. Ratios for this set of diastereomers were obtained upon transformation of the hydroxy sulfide to the epoxyalkyne as described in the following section. ^{1}H NMR

(300 MHz, $CDCl_3$) δ: 1.44−0.95 (m, 11H), 1.75 (m, 1H), 3.5 (m, 1H), 3.63 (m, 1H), 7.21−7.05 (m, 5H), OH was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ (14.1, 14.7), 22.4, 23.3, 32.5, 33.4, (42.8, 43.4), (65.3, 66.0), (74.0, 74.4), 82.1, 125.3, 125.7 (2), 128.5 (2), (137.1, 137.7). MS *m/z*: (M^+) calcd 248.1235, obsd 248.1216. Anal. Calcd. for $C_{15}H_{20}OS$: C, 72.53; H, 8.12. Found: C, 72.81; H, 7.91.

4. Analysis of Isolated Products Obtained from Coupling of 16 with α-Chloropropargyl Phenyl Sulfide (11). Separation of diastereomers was obtained by radial chromatography (elution with 50:1 hexanes−ethyl acetate) to give the hydroxy sulfides as colorless oils.

Syn Isomer. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.55−1.23 (m, 11H), 1.91 (d, $J = 1.9$ Hz, 1H), 3.50 (m, 1H), 3.60 (dd, $J = 1.9$, 6.9 Hz, 1H), 7.18−7.02 (m, 5 H), OH proton was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.4, 24.6, 25.3, 25.9, 27.4, 34.0, 41.2, 66.1, 77.3, 84.0, 124.9, 126.6 (2), 128.7, 129.0, 135.8. MS *m/z*: (M^+) calcd 260.1235, obsd 260.1226. Anal. Calcd for $C_{16}H_{20}OS$: C, 73.80; H, 7.74. Found: C, 73.99; H, 7.61.

Anti Isomer. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.55−1.23 (m, 11H), 1.96 (d, $J = 1.7$ Hz, 1H), 3.50 (m, 1H), 3.65 (dd, $J = 1.7$, 3.7 Hz, 1H), 7.18−7.02 (m, 5 H), OH proton was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.3, 24.4, 25.3, 25.5, 27.4, 33.1, 40.6, 66.1, 76.2, 83.0, 124.7, 126.6 (2), 128.8, 129.0, 135.8. MS *m/z*: (M^+) calcd 260.1235, obsd 260.1244. Anal. Calcd for $C_{16}H_{20}OS$: C, 73.80; H, 7.74. Found: C, 73.41; H, 7.59

4. Analysis of Product Mixture Obtained from Coupling of 17 with α-Chloropropargyl Phenyl Sulfide (11). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.80 (d, $J = 1.8$ Hz, 1H), 3.95 (dd, $J = 1.7$, 8.3 Hz, 0.33H), 4.04 (dd, $J = 1.7$, 5.2 Hz, 0.67H), 4.83 (m, 1H), 7.19−7.04 (m, 7H), 7.21 (m, 2H), OH proton was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 44.8, (67.7, 68.1), 77.6, (86.7, 87.0), 124.8, 125.3 (2), 127.7 (3), (127.9, 128.1), 129.1 (2), 123.7, 136.0, 139.1. MS *m/z*: (M^+) calcd 288.0376, obsd 288.0397. Anal. Calcd for $C_{16}H_{13}ClOS$: C, 66.54; H, 4.54. Found: C, 66.50; H, 4.57.

5. Analysis of Isolated Products Obtained from Coupling of 18 with α-Chloropropargyl Phenyl Sulfide (11). Separation of diastereomers was obtained by radial chromatography (elution with 50:1 hexanes−ethyl acetate) to give the hydroxy sulfides as colorless oils.

Syn Isomer. ^1H NMR (300 MHz, $CDCl_3$) δ 1.77 (d, $J =$ 1.8H), 3.95 (dd, $J = 1.8$, 8.2 Hz, 1.0H), 4.75 (m, 1H), 6.67 (m, 2H), 7.03 (m, 2H, 7.21−7.06 (m, 5H), OH proton was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.7, 67.7, 77.6, 86.7, 115.7 (2), 124.8, 125.3 (2), 127.7 (3), 127.8, 134.1, 134.9, 156.2. MS *m/z*: (M^+) calcd 270.0175, obsd 270.1069. Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 71.13; H, 5.26.

Anti Isomer. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.80 (d, $J =$ 1.8, 1H), 4.06 (dd, $J = 1.8$, 4.1 Hz, 1.0H), 4.75 (m, 1H), 6.65 (m, 2H), 7.03 (m, 2H, 7.25−7.09 (m, 5H), OH proton was not detected. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 43.9, 67.4, 77.2, 86.2, 115.1 (2), 125.0, 125.3 (2), 127.4 (3), 127.8, 133.9, 134.5, 155.7. MS *m/z*: (M^+) calcd 270.0175, obsd 270.1057. Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 71.01; H, 5.24.

IV. Coupling Procedures Using Indium Intermediates in a Water/Dimethylformamide Mixture as Solvent. A. Coupling of Benzaldehyde (10) with α-Chloropropargyl Phenyl Sulfide (11) Using Indium Metal in a Water/Dimethylformamide Mixture. The general procedure was followed as described in B. Purification was accomplished by flash chromatography on silica gel (elution with 40:1 hexanes−ethyl acetate) to give a mixture of hydroxy sulfides as a light yellow oil. Analysis was carried out in the manner specified for section III. A. Relevant ^1H NMR shifts (δ): 4.05 (dd, $J =$ 1.6, 8.1 Hz, 0.2H), 4.12 (dd, $J = 1.6$, 5.1, 0.8H).

B. Coupling of Aldehydes 1, 8, and 15−18 with α-Chloropropargyl Phenyl Sulfide (11) Using Indium Metal in a Water/Dimethylformamide Mixture. Processing and analysis of these reactions proceeded in the manner described above for **10** in section III.

1. Analysis of Product Mixture Obtained from Coupling of 1 with α-Chloropropargyl Phenyl Sulfide (11). Relevant ^1H NMR shifts (δ): 3.67 (dd, $J = 1.9$, 7.2 Hz, 0.32H), 3.73 (dd, $J = 1.9$, 4.2 Hz, 0.68H).

2. Analysis of Product Mixture Obtained from Coupling of 8 with α-Chloropropargyl Phenyl Sulfide (11). Relevant ^1H NMR shifts (δ): 3.58 (dd, $J = 2.1$, 7.6 Hz, 0.26H), 3.69 (dd, $J = 2.1$, 4.7 Hz, 0.74H).

3. Analysis of Product Mixture Obtained from Coupling of 15 with α-Chloropropargyl Phenyl Sulfide (11). Separation proceeded in the same manner as described above; however, separation was not obtained, and the ^1H NMR was not conclusive. Ratios for this set of diastereomers were obtained upon transformation of the hydroxy sulfide to the epoxyalkyne as described in the following section.

4. Analysis of Isolated Products Obtained from Coupling of 16 with α-Chloropropargyl Phenyl Sulfide (11). Separation of diastereomers was obtained by radial chromatography (elution with 50:1 hexanes−ethyl acetate) to give the hydroxy sulfides as colorless oils. Relevant ^1H NMR shifts (δ): syn isomer (3.60 (dd, $J = 1.9$, 6.9 Hz, 1H)); anti isomer (3.65 (dd, $J = 1.7$, 3.7 Hz, 1H)).

5. Analysis of Product Mixture Obtained from Coupling of 17 with α-Chloropropargyl Phenyl Sulfide (11). Relevant ^1H NMR shifts (δ): 3.95 (dd, $J = 1.7$, 8.3 Hz, 0.35H), 4.04 (dd, $J = 1.7$, 5.2 Hz, 0.65H).

6. Analysis of Isolated Products Obtained from Coupling of 18 with α-Chloropropargyl Phenyl Sulfide (11). Separation of diastereomers was obtained by radial chromatography (elution with 50:1 hexanes−ethyl acetate) to give the hydroxy sulfides as colorless oils. Relevant ^1H NMR shifts (δ): syn isomer (3.95 (dd, $J = 1.8$, 8.2 Hz, 1.0H)), anti isomer (4.06 (dd, $J = 1.8$, 4.1 Hz, 1.0H)).

V. Coupling Procedures Using Indium Intermediates and $InCl_3$ in Water. A. Coupling of Benzaldehyde (10) with α-Chloropropargyl Phenyl Sulfide (11) Using Indium Metal and $InCl_3$ in Water. The general procedure was followed as described in A with the exception that 1 mmol of $InCl_3$ was added to the reaction mixture for every 1 mmol of aldehyde used. Purification was accomplished by flash chromatography on silica gel (elution with 40:1 hexanes−ethyl acetate) to give a mixture of hydroxy sulfides as a light yellow oil.Relevant ^1H NMR shifts (δ): 4.05 (dd, $J = 1.6$, 8.1 Hz, 0.78H), 4.12 (dd, $J = 1.6$, 5.1 Hz, 0.22H).

B. Coupling of Aldehydes 1, 8, and 15−18 with α-Chloropropargyl Phenyl Sulfide *(11)* Using Indium Metal in a Water/Dimethylformamide Mixture. Processing and analysis of these reactions proceeded in the manner described above for **10** in section III.

1. Analysis of Product Mixture Obtained from Coupling of 1 with α-Chloropropargyl Phenyl Sulfide (11). Relevant ^1H NMR shifts (δ): 3.67 (dd, $J = 1.9$, 7.2 Hz, 0.77H), 3.73 (dd, $J = 1.9$, 4.2 Hz, 0.23H).

2. Analysis of Product Mixture Obtained from Coupling of 8 with α-Chloropropargyl Phenyl Sulfide (11). Relevant ^1H NMR shifts (δ): 3.58 (dd, $J = 2.1$, 7.6 Hz, 0.68H), 3.69 (dd, $J = 2.1$, 4.7 Hz, 0.32H).

3. Analysis of Product Mixture Obtained from Coupling of 15 with α-Chloropropargyl Phenyl Sulfide (11). Separation proceeded in the same manner as described above; however, separation was not obtained, and the ^1H NMR was not conclusive. Ratios for this set of diastereomers were obtained upon transformation of the hydroxy sulfide to the epoxyalkyne as described in the following section.

4. Analysis of Isolated Products Obtained from Coupling of 16 with α-Chloropropargyl Phenyl Sulfide (11). Separation of diastereomers was obtained by radial chromatography (elution with 50:1 hexanes−ethyl acetate) to give the hydroxy sulfides as colorless oils. Relevant ^1H NMR shifts (δ): syn isomer (3.60 (dd, $J = 1.9$, 6.9 Hz, 1H)); anti isomer (3.65 (dd, $J = 1.7$, 3.7 Hz, 1H)).

5. Analysis of Product Mixture Obtained from Coupling of 17 with α-Chloropropargyl Phenyl Sulfide (11). Relevant ^1H NMR shifts (δ): 3.95 (dd, $J = 1.7$, 8.3 Hz, 0.66H), 4.04 (dd, $J = 1.7$, 5.2 Hz, 0.33H).

6. Analysis of Isolated Products Obtained from Coupling of 18 with α-Chloropropargyl Phenyl Sulfide (11).

Separation of diastereomers was obtained by radial chromatography (elution with 50:1 hexanes−ethyl acetate) to give the hydroxy sulfides as colorless oils. Relevant ^{1}H NMR shifts (δ): syn isomer (3.95 (dd, J = 1.8, 8.2 Hz, 1.0H)); anti isomer (4.06 (dd, J = 1.8, 4.1 Hz, 1.0H)).

VI. Coupling Procedures Using Indium Intermediates and InCl$_3$ in a Water/Dimethylformamide Mixture. A. Coupling of Benzaldehyde (10) with α-Chloropropargyl Phenyl Sulfide Using Indium Metal and InCl$_3$ in a Water/Dimethylformamide Mixture. The general procedure was followed as described in B with the exception that 1 mmol of InCl$_3$ was added to the reaction mixture for every 1 mmol of aldehyde used. Purification was accomplished by flash chromatography on silica gel (elution with 40:1 hexanes−ethyl acetate) to give a mixture of hydroxy sulfides as a light yellow oil.

Processing and analysis of these reactions proceeded in the manner described above for **10** in section III. Relevant ^{1}H NMR shifts (δ): 4.05 (dd, J = 1.6, 8.1 Hz, 0.88H), 4.12 (dd, J = 1.6, 5.1, 0.12H).

B. Coupling of Aldehydes 1, 8, and 15−18 with α-Chloropropargyl Phenyl Sulfide *(12)* Using Indium Metal in a Water/Dimethylformamide Mixture. 1. Analysis of Product Mixture Obtained from Coupling of 1 with α-Chloropropargyl Phenyl Sulfide (11). Relevant ^{1}H NMR shifts (δ): 3.67 (dd, J = 1.9, 7.2 Hz, 0.76H), 3.73 (dd, J = 1.9, 4.2 Hz, 0.24H).

2. Analysis of Product Mixture Obtained from Coupling of 8 with α-Chloropropargyl Phenyl Sulfide (11). Relevant ^{1}H NMR shifts (δ): 3.58 (dd, J = 2.1, 7.6 Hz, 0.90H), 3.69 (dd, J = 2.1, 4.7 Hz, 0.10H).

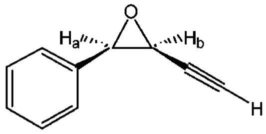
3. Analysis of Product Mixture Obtained from Coupling of 15 with α-Chloropropargyl Phenyl Sulfide (11). Separation proceeded in the same manner as described above; however, separation was not obtained, and the ^{1}H NMR was not conclusive. Ratios for this set of diastereomers were obtained upon transformation of the hydroxy sulfide to the epoxyalkyne as described in the following section.

4. Analysis of Isolated Products Obtained from Coupling of 16 with α-Chloropropargyl Phenyl Sulfide (11). Separation of diastereomers was obtained by radial chromatography (elution with 50:1 hexanes−ethyl acetate) to give the hydroxy sulfides as colorless oils. Relevant ^{1}H NMR shifts (δ): syn isomer (3.60 (dd, J = 1.9, 6.9 Hz, 1H)); anti isomer (3.65 (dd, J = 1.7, 3.7 Hz, 1H)).

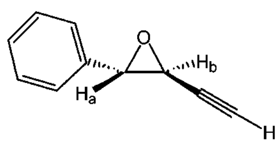
5. Analysis of Product Mixture Obtained from Coupling of 17 with α-Chloropropargyl Phenyl Sulfide (11). Relevant ^{1}H NMR shifts (δ): 3.95 (dd, J = 1.7, 8.3 Hz, 0.63H), 4.04 (dd, J = 1.7, 5.2 Hz, 0.37H).

6. Analysis of Isolated Products Obtained from Coupling of 18 with α-Chloropropargyl Phenyl Sulfide (11). Separation of diastereomers was obtained by radial chromatography (elution with 50:1 hexanes−ethyl acetate) to give the hydroxy sulfides as colorless oils. Relevant ^{1}H NMR shifts (δ): syn isomer (3.95 (dd, J = 1.8, 8.2 Hz, 1.0H)); anti isomer (4.06 (dd, J = 1.8, 4.1 Hz, 1.0H)).

VII. Formation of Epoxy Alkyne Compounds from Hydroxy Sulfides. A. Use of Trimethyloxonium Tetrafluoroborate. 1. Formation of 2-Ethynyl-3-phenyloxirane (19) from the Hydroxy Sulfide Precursor. A solution of the hydroxy sulfide mixture (100 mg 0.394 mmol) in dichloromethane (8 mL) was treated with trimethyloxonium tetrafluoroborate (66 mg (0.435 mmol). The solution was stirred at room temperature for 8 h and diluted with 7% sodium hydroxide solution (aqueous, 5 mL). After 20 min of stirring, the separated organic layer was dried and concentrated. Purification was accomplished by radial chromatography on silica gel (elution with 80:1 hexanes−ethyl acetate) to give a mixture of diastereomers as a colorless oil in an 8.8:1.2 ratio. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.45 (d, J = 1.8 Hz, 1H), 3.57 (dd, J = 1.8, 2.5 Hz, 0.12H), 3.71 (d, J = 2.5 Hz 0.12H), 3.99 (dd, J = 1.8, 4.6 Hz, 0.88H), 4.15 (d, J = 4.6 Hz, 0.88H), 7.21−7.19 (m, 5H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: (50.1, 50.3), (62.1, 62.5), (66.3, 66.7), (87.1, 87.5), (125.4 (2), 126.1 (2)), 128.2, 128.4, (128.9, 131.2), 137.5. MS *m/z*: (M$^+$) calcd 144.0575, obsd 144.0462. Anal. Calcd for C$_{10}$H$_8$O: C, 83.31; H. Found: C, 83.29; H, 5.55.



Hb : δ 3.99 ($J_{b,a}$ = 4.6 Hz)



Hb : δ 3.57 ($J_{b,a}$ = 2.5 Hz)

2. Formation of 20−25 from the Hydroxy Sulfide Precursor. Processing and analysis of these reactions proceeded in the manner described above for **19** in section VII.

a. Analysis of Product Mixture of 2-Ethynyl-3-styryloxirane (20). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.35 (d, J = 1.9 Hz, 0.10H), 2.50 (d, J = 1.9 Hz, 0.90H), 3.20, (dd, J = 1.9, 2.3 Hz, 0.10H), 3.61 (dd, J = 1.9, 4.1 Hz, 0.90H), 6.25 (m, 1H), 6.62 (m, 1H), 7.31−7.10 (m, 5H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: (47.9, 48.2), (57.5, 58.0), (66.9, 67.3), (87.1, 88.0), (126.5 (2), 127.1 (2)), 127.3, 127.7, 127.8, 128.4 (2), (135.0, 136.1). MS *m/z*: (M$^+$) calcd 170.0732, obsd 170.0687. Anal. Calcd for C$_{12}$H$_{10}$O: C, 84.68; H, 5.92. Found: C, 84.57; H, 5.96.

b. Analysis of Product Mixture of 2-Ethynyl-3-pent-1-enyloxirane (21). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.97−1.00 (m, 7H), 2.43 (m, 1H), 3.2 (m, 1H), 3.45 (dd, J = 2.0, 2.3 Hz, 0.23H), 3.60 (dd, J = 2.0, 4.4 Hz, 0.77H), 5.65 (m, 1H, 5.70 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 14, 23.3, 25.7, 47.9, (57.7, 5.1), (65.9, 66.8), (84.7, 85.2), (127.8, 128.3), (128.9, 129.6). MS *m/z*: (M$^+$) calcd 136.0888, obsd 136.0905. Anal. Calcd for C$_9$H$_{12}$O: C, 79.37; H, 8.88. Found: C, 79.46; H, 8.91.

c. Analysis of Product Mixture of 2-(4-Chlorophenyl)-3-ethynyloxirane (22). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.49 (d, J = 1.8 Hz, 0.33H), 2.55 (d, J = 1.9 Hz, 0.66H), 3.73 (dd, J = 1.8, 2.4 Hz, 0.33H), 3.77 (m, 1H), 4.11 (dd, J = 1.9, 4.0 Hz, 0.66H), 7.14 (m, 2H), 7.19 (m, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: (49.9, 50.5), (62.6, 63.4), (66.9, 67.3), (84.9, 85.4), (126.8 (2), 127.1 (2)), (127.5 (2), 128.9 (2)), 133.5, (135.8, 136.2). MS *m/z*: (M$^+$) calcd 178.0815, obsd 178.0884. Anal. Calcd for C$_{10}$H$_7$ClO: C, 67.24; H, 3.95. Found: C, 67.19; H, 3.97.

d. Analysis of 2-(4-Hydroxyphenyl)-3-ethynyloxirane (23). Isomers were separated during the coupling reaction (see section III. B. 6). **Syn Isomer.** ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.51 (d, J = 1.8 Hz, 1H), 3.75 (d, J = 4.3 Hz, 1H), 4.15 (dd, J = 1.8, 4.3 Hz, 1H), 6.64 (m, 2H), 7.0 (m, 2H), OH proton not detected. ^{13}C NMR (75 MHz, CDCl$_3$) δ 51.0, 62.7, 67.7, 84.1 115.5 (2), 125.7 (2), 130.5, 156.8. MS *m/z*: (M$^+$) calcd 160.0524, obsd 160.0491. Anal. Calcd for C$_{10}$H$_8$O$_2$: C, 74.99; H, 5.03. Found: C, 75.05; H, 4.99.

Anti Isomer. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.50 (d J = 1.8 Hz, 1H), 3.71 (d, J = 2.0 Hz, 1H), 3.81 (dd, J = 1.8, 2.0 Hz, 1H), 6.62 (m, 2H), 7.3 (m, 2H), OH proton not detected. ^{13}C NMR (75 MHz, CDCl$_3$) δ: 51.9, 63.4, 68.1, 84.9, 116.0 (2), 126.8 (2), 130.1, 157.0. MS *m/z*: (M$^+$) calcd 160.0524, obsd 160.0613. Anal. Calcd for C$_{10}$H$_8$O$_2$: C, 74.99; H, 5.03. Found: C, 74.89; H, 5.01.

e. Analysis of 2-Cyclohexyl-3-ethynyloxirane (24). Isomers were separated during the coupling reaction (see section III, B. 2). **Syn Isomer.** ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.79−1.24 (m, 11H), 2.39 (d, J = 1.6 Hz, 1H), 2.5 (m, 1H), 3.59, (dd, J = 1.6, 4.4 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 24.5, 24.6, 26.8, 27.0, 27.4, 29.8, 45.5, 60.4, 66.0, 81.5. MS *m/z*: (M$^+$) calcd 150.1045, obsd 150.1091. Anal. Calcd For C$_{10}$H$_{14}$O: C, 79.96; H, 9.39. Found: C, 79.90; H, 9.31.

Anti Isomer. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.70−1.24 (m, 11H), 2.43 (d, j = 1.6 Hz, 1H), 2.5 (m, 1H), 3.35 (dd, J = 1.6, 2.0 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 24.5, 24.6, 26.7, 27.0, 27.5, 29.8, 46.0, 61.3, 65.9, 82.8. MS *m/z*: (M$^+$) calcd 150.1045, obsd 150.1103. Anal. Calcd for C$_{10}$H$_{14}$O: C, 79.96; H, 9.39. Found: C, 79.89; H, 9.32.

f. Analysis of Product Mixture of 2-Ethynyl-3-pentyloxirane (25). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.42−0.91 (m, 11H), 2.45 (m, 2H), 3.45 (dd,J = 1.6, 2.1 Hz, 0.47H), 3.64 (dd, *J* = 1.6, 4.4 Hz, 0.53H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 23.1, 25.1, 30.0, 32.5, (47.0, 47.5), (54.6, 54.9), (65.9, 66.7), (85.7, 86.2). MS *m*/*z*: (M^+) calcd 138.1045 obsd 138.0997. Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.29; H, 10.27.

A. Use of TlOEt. 1. Formation of 19 from the Hydroxy Sulfide Precursor. A solution of the hydroxy sulfide mixture (100 mg 0.394 mmol) in chloroform (8 mL) was treated with TlOEt (130 mg, 0.516 mmol). The solution was stirred at room temperature for 10 h and diluted with ether. After 20 min of stirring, the insolubles were removed by filtration through a short Celite pad. The resulting organic solution was washed with a saturated $NaHCO_3$ solution (aqueous) and a saturated NaCl solution (aqueous). The organic layer was then dried and concentrated. Purification and analysis of products proceeded in the manner previously described (see section VII, A).

Acknowledgment. Financial support received from a Pfizer Undergraduate Research Award Grant and by the Trinity College Internal Grant Foundation is greatly acknowledged.

JO015992L