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# Use of *N*-Methylformamide as a Solvent in Indium-Promoted Barbier Reactions en Route to Enediyne and Epoxy Diyne Formation: Comparison of Rate and Stereoselectivity in C−C Bond-Forming Reactions with Water

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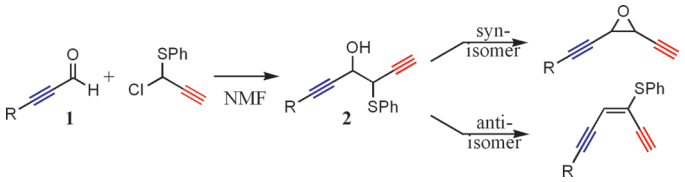


Indium-promoted coupling reactions between propargyl aldehydes (**1**) and α-chloropropargylphenyl sulfide are reported. Although water has been shown to accelerate indium metal promoted reactions, the reverse pattern was observed in this series. Use of *N*-methylformamide (NMF), which has not previously been a solvent known for use in indium-promoted reactions, afforded an acceleration of these Barbier-style reactions compared to water. Indium-promoted reactions in this study also showed excellent regiocontrol and good stereocontrol, allowing for easy entry into the formation of epoxydiyne and enediyne skeletal structures. This paper also describes use of the Barbier Coupled product (**2**) as a new, and easy, entry into the formation of enediyne and epoxydiyne skeletal structures.

## Indroduction

Many studies over the past 15 years have focused on discovering solvents that help promote efficient C−C bond formation under benign reaction conditions.[1,2] New solvents in Diels−Alder[2] and Barbier[3,4] reactions have been sought to help streamline the one-pot transformations further, reducing synthetic steps and organic waste. Polar media often accelerate reactions of this type which has led to the use of water as an acceptable solvent for such organic conversions.[1−4] Recent contributions from our laboratory to this field have centered on coupling reactions between propargyl aldehydes and allyl or propargyl halides under Barbier conditions to form homoallylic and homopropargylic propargyl alcohols.[5a,b] These compounds find wide use as synthetic templates and show a propensity for oxy-Cope rearrangements (Scheme 1).[5,6]

The use of α-chloropropargylphenyl sulfide (**4**), coupled with a propargyl aldehyde should offer an easy route into

(1) For reviews and examples, see: (a) Auge, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739. (b) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (c) Araki, S.; Hirashita, T. In *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 323−386. (d) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P., Williamson, T., Eds.; Oxford University Press: New York, 1998. (e) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*: John Wiley & Sons: New York, 1997.

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(5) (a) Mitzel, T. M.; Wzorek, J.; Troutman, A.; Allegue, K. *J. Org. Chem.* **2007**, *72*, 3042. (b) Mitzel, T. M.; Palomo, C.; Jendza, K. *J. Org. Chem.* **2002**, *67*, 136. (c) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931 and references therein.

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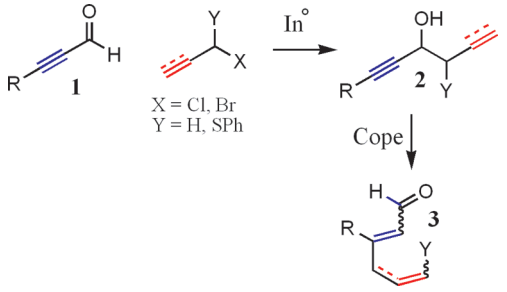
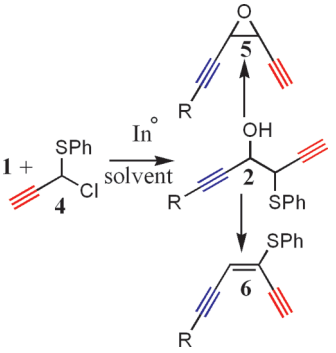
**SCHEME 1. Barbier Coupling Reactions of Propargyl Aldehydes and Allyl or Progrargyl Halides**




**SCHEME 2. Use of 4 To Form Enediyne and Epoxydiyne Skeletal Structures**




formation of enediyne and epoxydiyne skeletal structures (Scheme 2). Previous studies revealed that formation of **2** or **3** under indium-promoted Barbier conditions is solvent dependent.[5a,6] Use of an organic solvent for the coupling reaction results in a mixture of **2** and **3** while the use of water as a solvent yields **2** as the sole product.

There may be two reasons for this selectivity. It is possible that water protonates the coupled product to form **2** quickly, quenching the alkoxide intermediate, thereby suppressing the possible oxy-Cope pathway shown in Scheme 1. It may also be possible that the increased polarity of the solvent itself stabilizes the anion formed upon coupling, thus raising the relative rate of Cope rearrangement in this system. With a less polar, aprotic solvent, the anion will not be quenched, nor will it be stabilized to the same extent as witnessed in water. A combination of these phenomena may be why an oxy-Cope rearrangement occurs under less polar conditions, forming product **3** (Scheme 1). A coupling reaction between **1** and **4** (Scheme 2) was conducted under aqueous conditions to form **2** (Y = SPh), with good regioselectivity; however, the rate of this reaction is surprisingly slow. Although reactions of the type shown in Scheme 1 are reported in the literature to be accelerated by polar solvents such as water,[3−5] coupling reactions between **1** and **4**, as shown in Scheme 2, are quite slow. Indeed, when water is used as the solvent, reactions often require 10−36 h for completion. We believe there are two reasons behind the slow rate of reaction. First, when the reagents are mixed, a viscous, orange oil forms. This oil has a density greater than that of water so it is presumed to be an organometallic species formed by interaction of the indium metal with the halide species. We also believe the aldehyde species may be part of the complex as well. Isolation of the oil followed by workup in an acidic THF/$H_2O$ mixture leads to isolation of propargylphenyl sulfide and, to a smaller extent, the aldehyde. We surmise that low solubility of this organometallic complex leads to poor reagent mixing, slowing the Barbier coupling under aqueous conditions. Second, indium-promoted coupling reactions conducted in water become more acidic as the reaction proceeds.[1,5] We believe it is possible that the aldehyde is in equilibrium with its corresponding hydrate species, reducing the electrophilicity of the carbon center. A combination of these two reasons would lead to a decrease in the rate of reaction between **1** and **4** when conducted in an aqueous solvent. The reaction proceeds more quickly (8−12 h) in DMF, a less polar solvent, due to better solubility of all reagents, however, a mixture of **2** and **3** was isolated. It was originally expected that a mixture of water and DMF would lead to faster reaction times while still maintaining regiocontrol of product formation. The use of a water/DMF solvent system, however, resulted in a mixture of products with water constituting up to 50% v/v of the solvent system. When water exceeds 50% v/v of the solvent system, only product **2** is isolated, but the rate of reaction slows perceptively once again. To help expedite this reaction sequence, we began a search for solvent with polarity similar to, or greater than that of water. It was expected that an extremely polar organic solvent would promote the same type of acceleration normally witnessed in Barbier couplings carried out under aqueous conditions.[1−5] An organic solvent could also help solubilize the intermediate and reduce possible formation of the hydrate species, thus allowing for a faster coupling reaction to occur. If increased polarity stabilizes the anion formed by coupling of **1** and **4**, oxy-Cope rearrangement should also be suppressed.

With a dielectric constant of 186.9 at 25 °C,[7a,b] significantly greater than that of water (78.37[7]), and DMF (38.3[7b]), *N*-methylformamide (NMF) has found occasional use in previous reactions requiring polar organic solvents; however, it has historically found more widespread use as an organic reagent.[7,8] With a p$K_a$ of approximately 24,[7d] NMF is reactive under a range of organometallic reagent conditions, limiting its use as a solvent.[1−4] Indium-promoted coupling reactions, however, have been shown to be accelerated under aqueous conditions,[1] and the relative acidity of NMF, being higher than that of water, should not hinder the proposed Barbier couplings proposed within this paper. We

(6) For reviews and examples, see: (a) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765. (b) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: New York, 2001; pp 947−951. (c) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129. (d) Miao, W.; Chung, W. C.; Wu, Y.-D.; Chan, T. H. *J. Am. Chem. Soc.* **2004**, *125*, 13326. (e) White, B. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *135*, 14901–14904. (f) Santora, V. J.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 7976. (g) Viola, A.; MacMillan, J. H. *J. Am. Chem. Soc.* **1970**, *92*, 2404.

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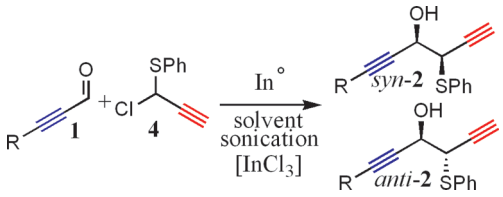
(8) A few representative examples of NMF use as a solvent: (a) Camerel, F.; Gabriel, J-C. P.; Batail, P.; Davidson, P.; Lemaire, B.; Schnutz, M.; Gulik-Krzywicki, T.; Bourgaux, C. *Nano Lett.* **2002**, *2*, 403. (b) Chassin, C.; Schmidt, E. A.; Hoffmann, H. M. R. *J. Am. Chem. Soc.* **1974**, *96*, 606. (c) Berger, S. K.; Powell, C. R.; Henning, B. D.; Furman, G. S.; Loffredo, W. M.; Rydberg, E. M.; Neubert, R. A.; Shoop, C. E.; Blauch, D. N. *J. Phys. Chem.* **1981**, *85*, 1236.

**TABLE 1. Comparison of NMF versus Water in Indium-Promoted Coupling of 1 and 2**[a]




| | R | solvent | ratio (syn/anti) | yield (%) | reaction time (h) |
|---|---|---|---|---|---|
| 1 | *n*-butyl | NMF | **25:75** | 92 | 3.5 |
| 2 | | $H_2O$ | 40:60 | 83 | 20.0 |
| 3 | | NMF/ $InCl_3$ | **85:15** | 93 | 4.0 |
| 4 | | $H_2O/InCl_3$ | 69:31 | 77 | 20.0 |
| 5 | phenyl | NMF | **20:80** | 91 | 5.0 |
| 6 | | $H_2O$ | **20:80** | 80 | 32.0 |
| 7 | | NMF/ $InCl_3$ | **85:15** | 93 | 5.5 |
| 8 | | $H_2O/InC1_3$ | 75:25 | 75 | 28.0 |
| 9 | TMS | NMF | 40:60 | 94 | 4.5 |
| 10 | | $H_2O$ | 50:50 | 70 | 17.5 |
| 11 | | NMF/ $InC1_3$ | 70:30 | 91 | 4.5 |
| 12 | | $H_2O/InC1_3$ | 60:40 | 72 | 20.0 |
| 13 | $TBSO(CH_2)_3$ | NMF | **15:85** | 87 | 5.0 |
| 14 | | $H_2O$ | 40:60 | 77 | 32.5 |
| 15 | | NMF/ $InCl_3$ | **90:10** | 89 | 5.5 |
| 16 | | H2O/$InC1_3$ | 70:30 | 71 | 36.0 |

[a]Reactions were run from 3 to 36 h under sonication. The ratio of reagent was as follows: 1.0:1.5:1.1 (aldehyde/halide/indium). The reaction was run at 0.1 M with respect to indium. In the Lewis acid catalyzed reaction, 10 molar % of the Lewis acid was used.

were especially intrigued by the fact that the dielectric constant of NMF increases to 220 as the temperature is lowered from 25 to 0 °C.[6,7] We were interested in examining what effect the increase in dielectric constant at lower temperature could have on a Barbier-style reaction of the type shown in Scheme 2 among others. This paper reports on the use of NMF in Barbier-style reactions with a focus on rates of reaction, stereochemistry, and its use to form enediyne and epoxydiyne skeletal structures.[9]

## Results and Discussion

**Reaction of Propargyl Aldehydes with α-Chloropropargylphenyl Sulfide.** Although NMF has characteristics similar to those of DMF, it also has characteristics similar to water, such as a polar X−H bond.[7] Thus, having found a very polar solvent with properties similar to both water and organic systems, we hypothesized that the 1,2-coupling product could be formed in high yield under short

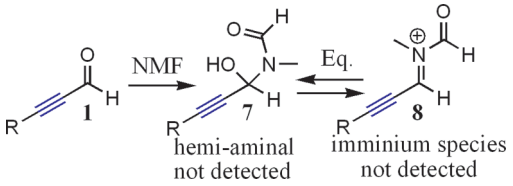



**FIGURE 1.** Possible formation of hemiaminal or imminium species.

reaction times. A series of reactions was set up to test this hypothesis.

As shown in Table 1, use of either water or NMF resulted in formation of the 1,2-product (**2**) solely with no trace of **3** detected in the product mixture. Although the yield of product was moderate to high in either solvent, product formation in reactions conducted in NMF proceeded at a much greater rate. We believe that there are two possible reasons behind the rate increase of coupling reactions carried out in NMF.

First, there is better mixing of reagents in NMF. All species completely dissolved in NMF, unlike what was observed for reactions in water. As such, we believe mixing is much more efficient, allowing the reaction to proceed at a faster rate. Second, there is increased solvent polarity. As discussed previously, increased solvent polarity has also been noted in many literature examples to lead to rate enhancement in indium-promoted Barbier reactions.[3−5] We believe a mixture of better solubility coupled with greater solvent polarity results in an additive effect toward increasing the rate of reactions conducted in NMF when compared to water. H-bonding capabilities of NMF may explain the greater regioselectivity for reactions conducted in NMF when compared to those observed in DMF and THF;[1,5,7] however, the H-bonding capacity of NMF is much lower than that of water.[7d] Increased solvent polarity, thus increasing the stability of the intermediate anion and raising the relative energy of the oxy-Cope rearrangement, may seem more likely at this time. In an effort to exclude the solvent as a direct participant in intermediate formation when NMF is used, NMR spectroscopy studies were performed to determine if a possible hemiaminal or imminium species was forming in situ (Figure 1). The imminium functionality carries a positive charge and would increase the electrophilicity of the reactive carbon. Mixing of **1** and NMF under sonication for periods of up to 24 h, however, revealed the presence of only **1** and NMF by NMR spectroscopy.

**Stereoselectivity of Reactions.** The presence or absence of a Lewis acid has shown to help control stereoselectivity in indium-promoted C−C bond-forming reactions.[5b,c,10] Previous studies in our laboratory have shown that the addition of indium(III) chloride as a Lewis acid favors formation of the *syn*-product in indium-promoted C−C bond-forming reactions between **4** and aldehyde functional groups.

In the absence of the Lewis acid, the *anti*-product is favored (Figure 2).[5b] It was our hope that similar effects would be witnessed in the present system, especially while using NMF as the reaction solvent, and we were pleased to see this trend continue. Absence of a Lewis acid in the reagent mixture favored a nonchelated pathway, leading to formation of *anti*-**2**.

(9) Epoxy diynes: (a) Baker, J. R.; Britton, T. H.; Caddick, S. *Org. Lett.* **2007**, *9*, 45. (b) Myers, A. G.; Glatthar, R.; Hamond, M.; Harrington, P. M.; Kuo, Y.; Liang, J.; Schaus, S. E.; Wu, Y.; Xiang, J.-N. *J. Am. Chem. Soc.* **2002**, *124*, 5380. (c) Kobayashi, S.; Reddy, R. S.; Sugiura, Y.; Sasaki, D.; Miyagawa, N.; Hirama, M. *J. Am. Chem. Soc.* **2001**, *123*, 2887. (d) Ando, T.; Ishii, M.; Kajiura, T.; Kameyama, T.; Miwa, K. 38th Symposium on the Chemistry of Natural Products, Japan, Symposium Papers, **1996**, p 487. Enediynes : (e) Johnson, H. D.; Thorson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 17662. (f) Van Lanen, S. G.; Shen, B. *Curr. Top. Med. Chem.* **2008**, *8*, 448. (g) DeVoss, J. J.; Townsend, C. A.; Ding, W.0D.; Morton, G. O.; Ellestad, G. A.; Zein, N.; Tabor, A. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9669. (h) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198.

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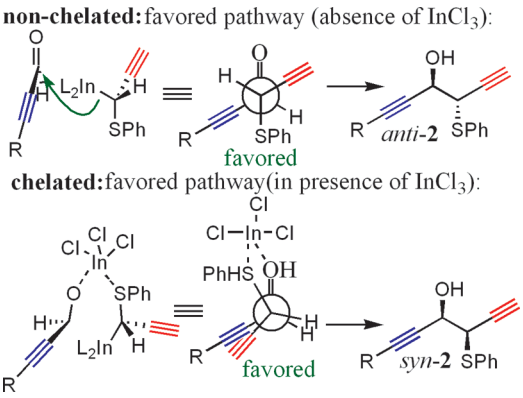


**FIGURE 2.** Use of indium chloride to control stereochemistry.[5b]

The presence of a Lewis acid in the reaction mixture favored a chelated pathway, leading to formation of *syn*-**2** (Figure 3).

Diastereoselectivities were determined either by direct measurement of vicinal coupling constants in the hydroxyl sulfide or by corresponding conversion to the epoxide compounds as shown in Figure 4.[11]

Entries 1, 5, and 13 (Table 1) describe reactions run in NMF in the absence of a Lewis acid. Good *anti*-selectivity is witnessed with ratios as high as 15:85 (*syn*/*anti*). In all cases, with the exception of R = phenyl, systems, with and without $InCl_3$, run in NMF gave better selectivity than systems run in water. Both systems showed poor selectivity when R = TMS for reasons of which we are not quite sure. When $InCl_3$ was added as a Lewis acid, the chelated route was favored in ratios as high as 90:10 (*syn*:*anti*, entry 15). *N*-Methylformamide was shown to increase the rate of reaction compared with water and offered better stereocontrol in the systems studied.

**Formation of Epoxydiyne and Enediyne Skeletal Structures.** Enediyne and epoxydiyne functionalities contain either a (*Z*)-3-ene-1,5-diyne or (*Z*)-3-epoxy-1,5-diyne unit which leads to their noted activity.[9] These unique functional groups cyclize to form a *p*-benzyne- or *p*-benzyne-like intermediate that interacts with DNA by abstracting hydrogen.[9] The DNA diradical then either couples with itself, or cleaves, stopping replication. Natural product enediyne and epoxydiynes have found use as anticarcinogenic compounds.[9] This area of study is slowed, however, by complicated access into the skeletal systems required.[9] Literature procedures that find use in epoxy alkyne formation such as halohydrin cylization,[12] *m*-CPBA,[13] or Oxone[14] have been shown to be successful, but limited examples are known with these systems at present.[12−15] Under the Barbier coupling conditions

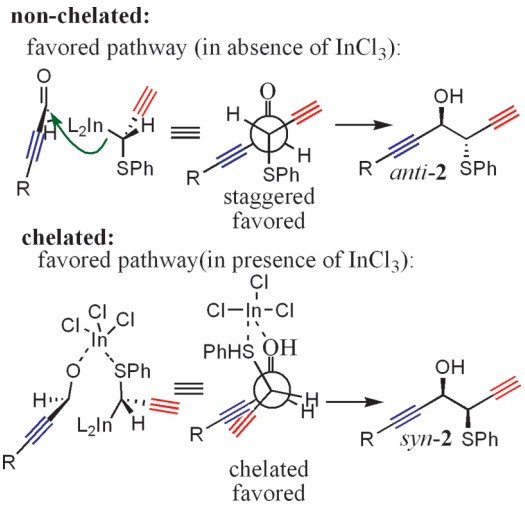


**FIGURE 3.** Nonchelated and chelated pathways.

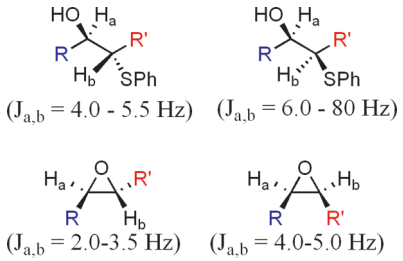


**FIGURE 4.** General *J* values for hydroxyl sulfides and epoxide structures.

described in this paper, formation of compound **2** offers an efficient and controlled method for the formation of either an enediyne or epoxydiyne skeletal structure under benign conditions by allowing easy conversion to either the *cis*-epoxydiyne (from *syn*-**2**, Scheme 3) or the *cis*-enediyne (from *anti*-**2**, Scheme 4). Facile synthesis of epoxydiyne and enediyne functional groups under the reported conditions would allow for their use as template structures in organic synthesis, opening access to more sophisticated units for further exploration. In the following pages, we describe the transformation of **1** into either an epoxydiyne (**5**) or enediyne (**6**) skeletal structure in two steps with high regio- and stereocontrol using NMF as a new solvent to form **2** under Barbier conditions, followed by a one-step transformation to yield either **5** or **6**.

As shown in Scheme 3, *syn*-**2** can adopt the correct conformation to form a *cis*-oxirane upon reaction with either $Me_3OBF_4$ or TlOEt. Conversion of the hydroxy sulfide starting material (**2**) to the epoxyalkyne product (**5**) was quite successful as shown in Table 2. In all cases, the propargyl group derived from the halide is preserved. This fact is worth mentioning as Barbier reactions with propargyl halides can lead to rearrangement of the organometallic intermediate into an allenyl product.[4,5,16] Reagent **4** has been previously shown to offer one of the few examples of a

(11) (a) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. M. *J. Org. Chem.* **1997**, *62*, 4293. (b) Sata, 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.

(12) Chemla, F.; Bernard, N.; Normant, J. F. *Tetrahedron Lett.* **1999**, *40*, 75.

(13) Examples : Normant J. F. *Tetrahedron*, **1991**, *47*, 1677 and ref. therein.

(14) Cao, G.-A.; Wang, Z. X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425 and ref. therein.

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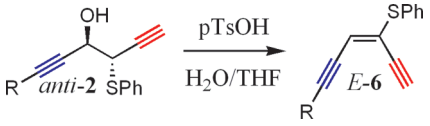
**TABLE 2. Conversion of *syn*-2 to *syn*-Epoxydiynes 5**

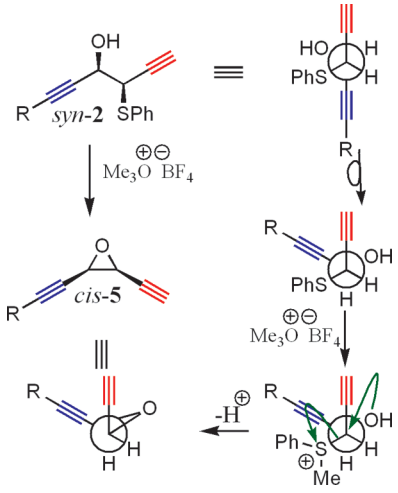

| | R | Ratio of **2** (syn:anti) | Ratio of **5** (syn:anti) | Yield % |
|---|---|---|---|---|
| 1 |  | 85:15 | 85:15 | 90 |
| 2 |  | 85:15 | 85:15 | 89 |
| 3 | | 75:25 | 75:25 | 90 |
| 4 | TMS | 70:30 | 70:30 | 72 |
| 5 | $TBSO(CH_2)_3$ | 90:10 | 90:10 | 83 |

**TABLE 3. Conversion of *anti*-2 into (*E*)-6 (*cis*-Enediyne)**




| | R | Ratio of **2** (syn:anti) | Ratio of **6** (*E*:*Z*) | Yield % |
|---|---|---|---|---|
| 1 |  | 25:75 | 73:27 | 87 |
| 2 |  | 0:100 | 97: 3 | 83 |
| 3 | | 20:80 | 77:23 | 85 |
| 4 | | 40:60 | 50:50 | 65 |
| 5 | TMS | 0:100 | 97: 3 | 65 |
| 6 | $TBSO(CH_2)_3$ | 15:85 | 82:18 | 80 |

**SCHEME 3. Pathway of Conversion of *cis*-Epoxydiyne (5) from *syn*-2**



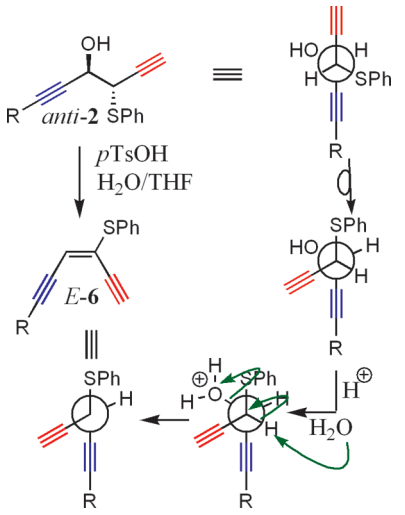

Barbier reaction with a propargyl halide where rearrangement does not occur.[5b] Use of TlOEt[17] gave yields similar to that of $Me_3OBF_4$[18] in all cases of oxirane formation, with stereoselectivity preserved under both sets of conditions.

Use of the *anti*-**2** allows formation of the (*E*)-alkene (the alkyne functional groups are *cis* to each other) functional group by the pathway shown in Scheme 4.

Formation of the enediyne product was possible under slightly acidic conditions. A catalytic amount of *p*-TsOH is added to *anti*-**2** in a mixture of water and THF (10% water) with stirring for 3−7 h. The reaction was also conducted under basic conditions after transformation of the OH group to a tosylate. Yields were quite low under basic conditions, presumably due to the competing acidity of the alkynyl proton, leading to decomposition and side product formation. Due to low yields, a transformation under basic conditions was not further explored during this study. Results of the acid-catalyzed conversion of *anti*-**2** to (*E*)-**6** are shown in Table 3. Yields for most systems were in the low 80% range.

(17) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 6116.
(18) (a) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1978**, *43*, 3803. (b) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 6116.

**SCHEME 4. Pathway of Conversion of *anti*-2 to (*E*)-Enediyne 6**




A slight amount of isomerization was witnessed under acidic conditions (about 3% of the product mixture), but overall, good stereocontrol was realized in these conversions, allowing for easy entry into the *cis*-enediyne ((*E*)-alkene) skeletal structure in a two-step sequence.

The assignment of *E*- and *Z*-isomers was made by comparison of the $\beta$-vinyl proton shift. Alignment of the $\beta$-vinyl proton and the heteroatom *cis* to each other gives rise to a lower field proton resonance than *trans* alignment of these two groups (Figure 5).[19] The assignments for the enediyne products are compared correctly with the stereochemistry of compounds **2** and **3** within this study.

Coupled with the original indium-promoted Barbier reaction, the transformation of starting materials **1** and **4** into enediyne or epoxydiyne compounds proceeded in two steps

(19) NMR shifts in *cis*- vs *trans*-enol ethers: (a) Giessert, A. J.; Brazis, N. J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3819. (b) Choi, J.; Imai, E.; Mihara, M.; Oderaotoshi, Y.; Minakata, S; Komatsu, M. *J. Org. Chem.* **2003**, *68*, 6164. (c) Trost, B. M.; Lavoie, A. *J. Am. Chem. Soc.* **1983**, *105*, 5075. (d) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324 and references therein.

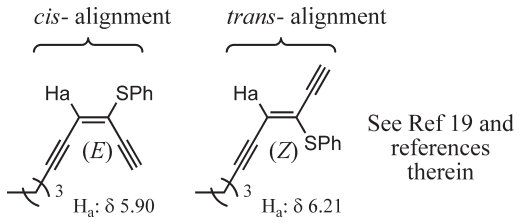



**FIGURE 5.** Representative $^1$H NMR shift when aligned *cis* and/or *trans* to the heteroatom.

in an overall 60−80% overall yield, offering an efficient, benign, and good-yielding formation of these important skeletal structures.

## Conclusion

Barbier reactions have become increasingly popular as a method form C−C bonds more efficiently. The use of *N*-methylformamide is shown to be a nice alternative to aqueous conditions in indium promoted coupling reactions between propargyl aldehydes (**1**) and α-chloropropargylphenyl sulfide (**4**). This paper introduces the use of NMF as s viable solvent in a Barbier coupling reaction, revealing increased rates and better selectivity when compared to reactions conducted in water and other organic solvents. The increased efficiency of the Barbier coupling reaction as described in this paper allows for facile formation of epoxy- and enediyne skeletal structures in an overall two-step procedure. The introduction of NMF as an alternative solvent in Barbier reactions will open new pathways to organic synthetic chemists. Further studies to test other halides and aldehyde functional groups under Barbier coupling reaction conditions in NMF are currently underway and will be reported in due time.

## 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 and reagents were used as purchased. Radial chromatography was performed using a Chromatatron.

**General Formation of Propargyl Aldehyde Compounds.**[20a] To a solution of 30 mmol of alkyne in 80 mL of THF that had been cooled to − 60 °C under nitrogen was added 15 mL of *n*-BuLi (2.0 M in THF) with stirring. To this solution was added *N*, *N*-dimethylformamide (4.66 mL, 60 mmol) dropwise over 10 min. The cooling bath was removed and the solution allowed to warm to 23 °C. After 20 min of further stirring, the solution was added to a mixture of 75 mL of *tert*-butyl methyl ether and 160 mL of 10% $KH_2PO_4$ solution which had been previously cooled to 0 °C. The entire solution was stirred at 0 °C for 30 min and then allowed to warm to room temperature. The aqueous and organic layers were separated. The organic layer was dried over $MgSO_4$, and the solvent removed under vacuum to give a clear oil.

(20) Examples of formation of propargyl aldehydes: (a) Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427. (b) Jackson, M. M.; Leverett, C.; Toczko, J. F.; Roberts, J. C. *J. Org. Chem.* **2002**, *67*, 5032. (c) Dixon, D. J.; Ley, S. V.; Tate, E. W. *Synlett* **1998**, 1093. (d) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301. (e) Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265. (f) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

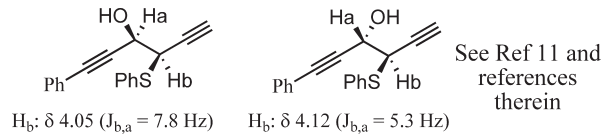
All propargyl aldehydes were used without further purification and could be stored at 0 °C for 2−3 weeks.

Yields for this reaction ranged from 85 to 95%.

**I. Coupling Procedures for Propargyl Aldehyde (1) with α-Chloropropargylphenyl Sulfide (4). I.a. General Procedure Using Water as Solvent.** A magnetically stirred solution of aldehyde (**1**) (2.0 mmol) in deionized water (22 mL) was treated with α-chloropropargylphenyl sulfide (702 mg, 3.0 mmol) and indium powder (228 mg, 2.0 mmol). The solution was allowed to proceed at room temperature until no **1** was seen (TLC analysis). Dichloromethane was added, and stirring was maintained for 30 min. The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to leave a dark yellow to brown oil. Purification was accomplished by flash chromatography or radial chromatography on silica gel (hexanes−ethyl acetate) to give a mixture of hydroxy sulfides (**2**)[11] as a light yellow oil.

**I.a.1. Use of 2-Heptynal (R = *n*-$C_4H_9$) with α-Chloropropargylphenyl Sulfide (4).** Processing and analysis of this reaction proceeded as described in section I.a. Purification was accomplished using radial chromatography on silica gel (40:1 hexanes−ethyl acetate) to give a mixture of diastereomeric hydroxy sulfides. It was not possible to determine stereoselectivity directly. Stereoselectivity was determined upon transformation to the epoxide product: yield = 471 mg (1.76 mmol) = 83%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.9−1.5 (m, 7H), 1.82 (d, $J$ = 1.7 Hz, 0.2H), 1.87 (d, $J$ = 1.6 Hz, 0.8H), 2.13 (t, $J$ = 6.5 Hz, 2H), 4.09 (m, 1H), 4.86 (m, 1H), 7.1−7.8 (m, 5H), the OH proton was not detected; $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 15.5, 18.2, 21.3, 34.2, (41.5, 42.9), (65.0, 66.1), 71.3, 78.5, 80.2, 84.7, 125.4, 126.1, 126.3, 127.6, 128.0, 136.4; MS $m/z$ ($M^+$) calcd 258.1078, obsd 258.0998. Anal. Calcd for $C_{16}H_{18}OS$: C, 74.38; H, 7.02. Found: C, 74.61; H, 6.99.

**I.a.2. Use of 3-Phenylpropynal (R = Phenyl) with α-Chloropropargylphenyl Sulfide (4).** Processing and analysis of this reaction proceeded as described in part I.a. Separation was accomplished using radial chromatography on silica gel (35:1 hexanes−ethyl acetate) allowing isolation of two hydroxyl sulfide diastereomers in a 20:80 *syn*/*anti* ratio: total yield = 489 mg (1.78 mmol) = 80%. *Anti* isomer: yield = 391 mg (1.41 mmol); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.94 (d, $J$ = 1.8 Hz, 1H), 4.10 (dd, $J$ = 1.8, 4.7 Hz, 1H), 5.11 (d, $J$ = 4.7 Hz, 1H), 7.2−7.7 (m, 10H), the OH proton was not detected; $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 43.8, 66.0, 68.0, 81.3, 87.2, 93.6, 121.7, 125.8 (2), 127.3 (3), 128.1, 128.3(2), 129.3, 129.5, 136.1. Anal. Calcd for $C_{18}H_{14}OS$: C, 77.66; H, 5.07. Found: C, 77.28; H, 5.18. *Syn* isomer: yield = 98 mg (0.37 mmol); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.83 (d, $J$ = 1.8 Hz, 1H), 3.95 (dd, $J$ = 1.8, 8.1 Hz, 1H), 4.95 (d, $J$ = 8.1 Hz, 1H), 7.2−7.7 (m, 10H), the OH proton was not detected; $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 44.1, 65.8, 68.0, 81.3, 87.2, 93.6, 121.7, 125.8 (2), 127.3 (3), 128.1, 128.3(2), 129.3, 129.5, 136.1.




$H_b$: δ 4.05 ($J_{b,a}$ = 7.8 Hz) $H_b$: δ 4.12 ($J_{b,a}$ = 5.3 Hz)

**I.a.3. Use of 3-Trimethylsilypropynal (R = TMS) with α-Chloropropargylphenyl Sulfide (4).** Processing and analysis of this reaction proceeded as described in section I.a. Separation was accomplished using radial chromatography on silica gel (35:1 hexanes−ethyl acetate) allowing isolation of two hydroxyl sulfide diastereomers in a 50:50 *syn*/*anti* ratio: total yield = 418 mg (1.54 mmol) = 70%; *Anti* isomer: yield = 209 mg (7.7 mmol); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.24 (s, 9H), 1.84 (d, $J$ = 1.6 Hz,

1H), 4.23 (dd, $J = 1.6$, 5.3 Hz, 1H), 4.80 (d, $J = 5.3$ Hz, 1H), 7.1−7.4 (m, 5H), the OH proton was not detected; $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 0.28(3), 44.4, 66.5, 67.5, 74.1, 84.3, 86.4, 125.0, 125.3, 126.5 (2), 127.3, 136.1; MS $m/z$ ($M^+$) calcd 274.0848, obsd 274.0819. Anal. Calcd for $C_{15}H_{18}OSSi$: C, 65.64; H, 6.61. Found: C, 65.17; H, 6.55. *Syn* isomer: yield = 209 mg (7.7 mmol) = 70%; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.24 (s, 9H), 1.79 (d, $J = 1.7$ Hz, 1H), 4.15 (dd, $J = 1.7$, 7.8 Hz, 1H), 4.69 (d, $J = 7.8$ Hz, 1H), 7.1−7.4 (m, 5H), the OH proton was not detected; $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 0.28(3), 44.1, 67.9, 68.1, 75.0, 83.2, 86.9, 125.0, 125.3, 126.5 (2), 127.3, 136.1.

**I.a.4. Use of 6-(*tert*-Butyldimethylsiloxy)-2-hexynal (R = $(CH_2)_3$OTBS) with α-Chloropropargylphenyl Sulfide (1).** Processing and analysis of this reaction proceeded as described in section I.a. Separation was accomplished using radial chromatography on silica gel (35:1 hexanes−ethyl acetate) to give a mixture of diastereomeric hydroxy sulfides: yield = 633 mg (1.69 mmol) = 77%; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.25 (s, 6H), 0.97 (s, 9H), 1.25 (m, 2H), 1.80−2.00 (m, 3H), 3.83 (t, $J = 6.5$, 2H), 4.11 (m, 1H), 4.99 (m, 1H), 7.1−7.4 (m, 5H), the OH proton was not detected; $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 0.28 (2), 14.5, 15.1, 21.8 (2), 21.9 33.4, 47.0, 64.6, 65.1, 67.9, 75.2, 81.9, 87.3, 125.4, 126.6 (2), 127.1, 128.4, 135.9; MS $m/z$ (M+) calcd 374.1736, obsd 365.1633 (loss of $H_2O$). It was not possible to determine stereoselectivity directly. Stereoselectivity was determined upon transformation to the epoxide product.

**I.b. General Procedure Using Water as Solvent with $InCl_3$ Added.** The general procedure was followed as described in section I.a with the exception that 1 mmol of $InCl_3$ was added to the reaction mixture for every 1 mmol of aldehyde used.

**I.b.1. Use of 2-Heptynal (R = *n*-$C_4H_9$) with α-Chloropropargylphenyl Sulfide (4).** Processing and analysis of this reaction proceeded as described in part I.b. Separation was accomplished using radial chromatography on silica gel (40:1 hexanes−ethyl acetate) to give a mixture of diastereomeric hydroxy sulfides. It was not possible to determine stereoselectivity directly. Stereoselectivity was determined upon transformation to the epoxide product: yield = 437 mg (1.63 mmol) = 77%. Analysis as shown in section I.a.1.

**I.b.2. Use of 3-Phenylpropynal (R = Phenyl) with α-Chloropropargylphenyl Sulfide (4).** Processing and analysis of this reaction proceeded as described in part I.b. Separation was accomplished using radial chromatography on silica gel (35:1 hexanes−ethyl acetate) allowing isolation of two hydroxyl sulfide diastereomers in a 75:25 *syn*/*anti* ratio: yield = total = 458 mg (1.65 mmol) = 75%. *Anti* isomer: yield = 115 mg (0.41 mmol); relevant $^1H$ NMR shifts (300 MHz, $CDCl_3$) $\delta$ 1.94 (d, $J = 1.8$ Hz, 1H), 4.12 (dd, $J = 1$,8, 4.5 Hz, 1H), 5.14 (d, $J = 4.5$ Hz, 1H). *Syn* isomer: yield = 343 mg (1.24 mmol); relevant $^1H$ NMR shifts (300 MHz, $CDCl_3$) $\delta$ 1.83 (d, $J = 1.8$ Hz, 1H), 3.92 (dd, $J = 1.8$, 8.0 Hz, 1H), 4.94 (d, $J = 8.1$ Hz, 1H)

**I.b.3. Use of 3-Trimethylsilypropynal (R = TMS) with α-Chloropropargylphenyl Sulfide (4).** Processing and analysis of this reaction proceeded as described in section I.b. Separation was accomplished using radial chromatography on silica gel (35:1 hexanes−ethyl acetate) allowing isolation of two hydroxyl sulfide diastereomers in a 60:40 *syn*/*anti* ratio: yield = total = 434 mg (1.58 mmol) = 72%. *Anti* isomer: yield = 174 mg (0.63 mmol); relevant $^1H$ NMR shifts (300 MHz, $CDCl_3$) $\delta$ 4.25 (dd, $J = 1.7$, 5.5 Hz, 1H), 4.77 (d, $J = 5.5$ Hz, 1H). *Syn* isomer: yield = 260 mg (0.95 mmol); relevant $^1H$ NMR shifts (300 MHz, $CDCl_3$) $\delta$ 4.15 (dd, $J = 1.5$, 7.8 Hz, 1H), 4.71 (d, $J = 7.8$ Hz, 1H).

**I.b.4. Use of 6-(*tert*-Butyldimethylsiloxy)-2-hexynal (R = $(CH_2)_3$OTBS) with α-Chloropropargylphenyl Sulfide (1).** Processing and analysis of this reaction proceeded as described in section I.b. Separation was accomplished using radial chromatography on silica gel (35:1 hexanes−ethyl acetate) to give a mixture of diastereomeric hydroxy sulfides. It was not possible to determine stereoselectivity directly. Stereoselectivity was determined upon transformation to the epoxide product: yield 583 mg (1.55 mmol) = 71%. Analysis as shown in section I.a.4.

**I.c. General Procedure Using *N*-Methylformamide as Solvent.** A magnetically stirred solution of aldehyde **1** (2.0 mmol) in NMF (22 mL) was treated with α-chloropropargylphenyl sulfide (702 mg, 3.0 mmol) and indium powder (228 mg, 2.0 mmol). The solution was allowed to proceed at room temperature until no **1** was seen (TLC analysis). Dichloromethane (20 mL) and water (30 mL) were added. Stirring was maintained for 30 min. The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with 1 N HCl (3 × 20 mL), dried over $MgSO_4$, and evaporated to leave a dark yellow to brown oil. Purification was accomplished by flash chromatography or radial chromatography on silica gel (hexanes−ethyl acetate) to give a mixture of hydroxy sulfides (**2**)[11] as a light yellow oil.

**I.c.1. Use of 2-Heptynal (R = *n*-$C_4H_9$) with α-Chloropropargylphenyl Sulfide (4).** Processing and analysis of this reaction proceeded as described in section I.c. Separation was accomplished using radial chromatography on silica gel (40:1 hexanes−ethyl acetate) to give a mixture of diastereomeric hydroxy sulfides. It was not possible to determine stereoselectivity directly. Stereoselectivity was determined upon transformation to the epoxide product: yield = 522 mg (2.02 mmol) = 92%. Analysis as shown in section I.a.1.

**I.c.2. Use of 3-Phenylpropynal (R = Phenyl) with α-Chloropropargylphenyl Sulfide (4).** Processing and analysis of this reaction proceeded as described in section I.c. Separation was accomplished using radial chromatography on silica gel (35:1 hexanes−ethyl acetate) allowing isolation of two hydroxyl sulfide diastereomers in a 20:80 *syn*/*anti* ratio: yield = total = 556 mg (2.00 mmol) = 91%. *Anti* isomer: yield = 445 mg (1.60 mmol); relevant $^1H$ NMR shifts (300 MHz, $CDCl_3$) $\delta$ 4.10 (dd, $J = 1.8$, 4.7 Hz, 1H), 5.11 (d, $J = 4.7$ Hz, 1H). *Syn* isomer: yield = 111 mg (0.40 mmol); relevant $^1H$ NMR shifts (300 MHz, $CDCl_3$) $\delta$ 3.95 (dd, $J = 1.8$, 8.1 Hz, 1H), 4.95 (d, $J = 8.1$ Hz, 1H).

**I.c.3. Use of 3-Trimethylsilypropynal (R = TMS) with α-Chloropropargylphenyl Sulfide (4).** Processing and analysis of this reaction proceeded as described in section I.c. Separation was accomplished using radial chromatography on silica gel (35:1 hexanes−ethyl acetate) allowing isolation of two hydroxyl sulfide diastereomers in a 40:60 *syn*/*anti* ratio: yield = total = 566 mg (2.06 mmol) = 94%. *Anti* isomer: yield = 340 mg (1.24 mmol); relevant $^1H$ NMR shifts (300 MHz, $CDCl_3$) $\delta$ 4.25 (dd, $J = 1.7$, 5.5 Hz, 1H), 4.77 (d, $J = 5.5$ Hz, 1H). *Syn* isomer: yield = 226 mg (0.82 mmol); relevant $^1H$ NMR shifts (300 MHz, $CDCl_3$) $\delta$ 4.15 (dd, $J = 1.5$, 7.8 Hz, 1H), 4.71 (d, $J = 7.8$ Hz, 1H).

**I.c.4. Use of 6-(*tert*-Butyldimethylsiloxy)-2-hexynal (R = $(CH_2)_3$OTBS) with α-Chloropropargylphenyl Sulfide (1).** Processing and analysis of this reaction proceeded as described in section I.c. Separation was accomplished using radial chromatography on silica gel (35:1 hexanes−ethyl acetate) to give a mixture of diastereomeric hydroxy sulfides. It was not possible to determine stereoselectivity directly. Stereoselectivity was determined upon transformation to the epoxide product: yield = 717 mg (1.91 mmol) = 87%. Analysis as shown in section I.a.4.

**I.d. General Procedure Using NMF as Solvent with $InCl_3$ Added.** The general procedure was followed as described in section I.c with the exception that 1 mmol of $InCl_3$ was added to the reaction mixture for every 1 mmol of aldehyde used.

**I.d.1. Use of 2-Heptynal (R = *n*-$C_4H_9$) with α-Chloropropargylphenyl Sulfide (4).** Processing and analysis of this reaction proceeded as described in section I.d. Separation was accomplished using radial chromatography on silica gel (40:1 hexanes−ethyl acetate) to give a mixture of diastereomeric hydroxy sulfides. It was not possible to determine stereoselectivity directly. Stereoselectivity was determined upon transformation

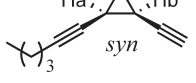
to the epoxide product: yield = 527 mg (2.05 mmol) = 93%. Analysis as shown in section I.a.1.

**I.d.2. Use of 3-Phenylpropynal (R = Phenyl) with α-Chloropropargylphenyl Sulfide (4).** Processing and analysis of this reaction proceeded as described in section I.d. Separation was accomplished using radial chromatography on silica gel (35:1 hexanes−ethyl acetate) allowing isolation of two hydroxyl sulfide diastereomers in a 85:15 *syn*/*anti* ratio: yield = total = 568 mg (2.05 mmol) = 93%. *Anti* isomer: yield = 85 mg (0.31 mmol); relevant $^1$H NMR shifts (300 MHz, $CDCl_3$) $\delta$ 4.13 (dd, $J$ = 1.8, 4.7 Hz, 1H), 5.08 (d, $J$ = 4.7 Hz, 1H). *Syn* isomer: yield = 483 mg (1.74 mmol); relevant $^1$H NMR shifts (300 MHz, $CDCl_3$) $\delta$ 3.92 (dd, $J$ = 1.8, 8.1 Hz, 1H), 4.97 (d, $J$ = 8.1 Hz, 1H).

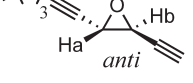
**I.d.3. Use of 3-Trimethylsilylpropynal (R = TMS) with α-Chloropropargylphenyl Sulfide (4).** Processing and analysis of this reaction proceeded as described in section I.d. Separation was accomplished using radial chromatography on silica gel (35:1 hexanes−ethyl acetate) allowing isolation of two hydroxyl sulfide diastereomers in a 70:30 *syn*/*anti* ratio: yield = total = 548 mg (2.00 mmol) = 91%. *Anti* isomer:: yield = 164 mg (0.60 mmol); relevant $^1$H NMR shifts (300 MHz, $CDCl_3$) $\delta$ 4.23 (dd, $J$ = 1.7, 5.5 Hz, 1H), 4.80 (d, $J$ = 5.5 Hz, 1H). *Syn* isomer: yield = 384 mg (1.40 mmol); relevant $^1$H NMR shifts (300 MHz, $CDCl_3$) $\delta$ 4.15 (dd, $J$ = 1.5, 7.8 Hz, 1H), 4.68 (d, $J$ = 7.8 Hz, 1H).

**I.d.4. Use of 6-(*tert*-Butyldimethylsiloxy)-2-hexynal (R = $(CH_2)_3$OTBS) with α-Chloropropargylphenyl Sulfide (1).** Processing and analysis of this reaction proceeded as described in section I.d. Separation was accomplished using radial chromatography on silica gel (35:1 hexanes−ethyl acetate) to give a mixture of diastereomeric hydroxy sulfides. It was not possible to determine stereoselectivity directly. Stereoselectivity was determined upon transformation to the epoxide product: yield = 732 mg (1.96 mmol) = 89%. Analysis as shown in section I.a.4.

**II. Formation of Epoxy Diyne Compounds from Hydroxy Sulfides. II.a. General Procedure Using Trimethyloxonium Tetrafluoroborate Reagent. II.a.1. Formation of 2-Ethynyl-3-hex-1-ynyloxirane.** A solution of the hydroxy sulfide mixture (85:15 *syn*/*anti*) (100 mg, 0.39 mmol) in dichloromethane (10 mL) was treated with trimethyloxonium tetrafluoroborate (90 mg (0.60 mmol). The solution was stirred at room temperature for 8 h and diluted with 7% sodium hydroxide solution (aqueous, 8 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 85:15 *syn*/*anti* ratio: yield = 52 mg (0.35 mmol) = 90%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.9 − 1.5 (m, 7H), 1.82 (d, $J$ = 1.8 Hz, 0.15H), 1.86 (d, $J$ = 1.9 Hz, 0.85H), 2.17 (m, 2H), 3.25 (d, $J$ = 4.6 Hz, 0.85H), 3.40 (d, $J$ = 2.3 Hz, 0.15H), 3.50 (dd, $J$ = 1.8, 2.3 Hz, 0.15H), 3.61 (dd, $J$ = 1.9, 4.6 Hz, 0.85H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (14.0, 14.1), (17.2, 17.4), 21.6, (31.7, 31.8), 44.5, (48.2, 48.3), 66.7, (77.5, 77.9), (79.5, 79.7), (85.2, 85.5). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.99; H, 8.19.




$H_b$: δ 3.61 ($J_{b,a}$ = 4.6 Hz)




$H_b$: δ 3.99 ($J_{b,a}$ = 2.3 Hz)

See Ref 11 and references therein

**II.a.2. Formation of 2-Ethynyl-3-phenylethylyloxirane.** A solution of the hydroxy sulfide mixture (85:15 *syn*/*anti*) (200 mg 0.72 mmol) in dichloromethane (20 mL) was treated with trimethyloxonium tetrafluoroborate (180 mg (1.20 mmol). The solution was stirred at room temperature for 12 h and diluted with 7% sodium hydroxide solution (aqueous, 15 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 100:1 hexanes−ethyl acetate) allowing isolation of two diastereomers as colorless oils in an 85:15 *syn*/*anti* ratio: yield = total = 110 mg (0.64 mmol) = 89%. *Anti* isomer: yield = 12 mg (0.07 mmol); $^1$H NMR (300 MHz, CDCl3) $\delta$ 2.44 (d, $J$ = 1.8 Hz, 1H), 3.51 (dd, $J$ = 1.8, 2.4 Hz, 1H), 3.97 (d, $J$ = 2.4 Hz, 1H), 7.15−7.25 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 48.2, 53.1, 66.2, 80.3, 87.3, 91.7, 123.5, 128.4 (2), 129.0, 133.1 (2). Anal. Calcd for $C_{12}H_8O$ = C, 85.69 H, 4.79. Found: C, 86.00 H, 4.71. *Syn* isomer: yield = 98 mg (0.57 mmol); $^1$H NMR (300 MHz, CDCl3) $\delta$ 2.43 (d, $J$ = 1.8 Hz, 1H), 3.46 (dd, $J$ = 1.8, 4.7 Hz, 1H), 4.15 (d, $J$ = 4.7 Hz, 1H), 7.15−7.23 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 48.7, 53.1, 66.5, 80.1, 87.3, 92.0, 123.0, 128.3 (2), 128.7, 132.3(2).

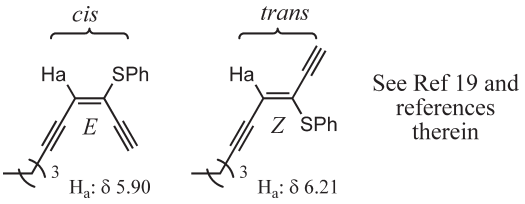
**II.a.3. Formation of 2-Ethynyl-3-(trimethylsilyl)ethylyloxirane.** A solution of the hydroxy sulfide mixture (70:30 *syn*/*anti*) (200 mg 0.73 mmol) in dichloromethane (20 mL) was treated with trimethyloxonium tetrafluoroborate (180 mg (1.20 mmol). The solution was stirred at room temperature for 12 h and diluted with 7% sodium hydroxide solution (aqueous, 15 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 100:1 hexanes−ethyl acetate) allowing isolation of two diastereomers as colorless oils in an 70:30 *syn*/*anti* ratio: yield = total = 108 mg (0.66 mmol) = 90%; *Anti* isomer: yield = 32 mg (0.30 mmol); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.13 (s, 9H); 2.21 (d, $J$ = 2.0 Hz, 1H), 3.25 (dd, $J$ = 2.0, 2.3 Hz, 1H), 3.55 (d, $J$ = 2.3 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 0.10 (3), 44.9, 49.9, 69.9, 81.7, 86.0, 102.0; MS $m/z$ ($M^+$) calcd = 164.0657, obsd = 164.0656. *Syn* isomer: yield = 76 mg (0.46 mmol); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.13 (s, 9H), 2.19 (d, $J$ = 2.0 Hz, 1H), 3.32 (dd, $J$ = 2.0, 4.9 Hz, 1H), 3.63 (d, $J$ = 4.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 0.10 (3), 45.1, 49.3, 70.1, 81.5, 85.6, 101.2.

**II.a.4. Formation of 2-Ethynyl-3-(*tert*-butyldimethylpropoxysilyl)ethylyloxirane.** A solution of the hydroxy sulfide mixture (90:10 *syn*/*anti*) (250 mg 0.67 mmol) in dichloromethane (20 mL) was treated with trimethyloxonium tetrafluoroborate (150 mg (1.00 mmol). The solution was stirred at room temperature for 12 h and diluted with 7% sodium hydroxide solution (aqueous, 12 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 100:1 hexanes−ethyl acetate) to give a mixture of two diastereomers as a colorless oil in a 90:10 *syn*/*anti* ratio: yield = 148 mg (0.56 mmol) = 83%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.22 (s, 6H); 0.97 (s, 9H), 1.27 (m, 2H), 1.8−2.0 (m, 3H), 3.23 (d, $J$ = 4.4 Hz, 0.9H), 3.31 (d, $J$ = 2.5 Hz, 0.1H), 3.53 (dd, $J$ = 1.9, 2.5 Hz, 0.1 Hz), 3.69 (dd, $J$ = 1.9, 4.4 Hz, 0.9H), 3.83 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 0.28 (2), 14.5, 14.7, 21.8 (2), (22.0, 22.3), (33.9, 34.2), (43.8, 44.0), (47.1, 47.9), (64.7, 65.0), 67.3, (78.7, 79.1), 81.8, (85.4, 85.8); MS $m/z$ ($M^+$) calcd = 264.1546, obsd = 264.1545. Anal. Calcd for $C_{15}H_{24}OSi$: C, 68.13; H, 9.15. Found: C, 67.79; H, 9.4.

**II.b. General Procedure Using TlOEt. Formation of 2-Ethynyl-3-phenylethylyloxirane. II.b.1. Formation of 2-Ethynyl-3-phenylethylyloxirane.** A solution of the hydroxy sulfide mixture (85:15 *syn*/*anti*) (200 mg 0.72 mmol) in chloroform (20 mL) was treated with TlOEt (234 mg, 0.93 mmol). The solution was stirred at room temperature for 15 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 (aq) and a saturated NaCl solution (aq). The organic layer was dried and concentrated. Purification and analysis of products proceeded in the manner previously described (section II.a).

Subsequent hydroxy sulfides were treated in a fashion similar to that in II.b.1 and analyzed in the manner previously described in section II.a.

**III. Formation of Enediyne Compounds from Hydroxy Sulfides. III.a. General Procedure: Acid Catalyzed Conditions. III.a.1. Formation of 6-Butylhex-3-ene-1,5-diyne-3-phenyl Sulfide.** A solution of the hydroxy sulfide mixture (25:75 *syn*/*anti*) (100 mg, 0.39 mmol) in a 9:1 THF/$H_2O$ mixture (10 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid . The solution was stirred at room temperature for 8−12 h and diluted with 10% sodium bicarbonate solution (aqueous, 10 mL). After 5 min of stirring, 20 mL of dichloromethane was added to the solution with stirring for 10 min. The separated aqueous layer was extracted with 3×10 mL of dichloromethane. The organic layers were combined, washed with 3 × 10 mL of water, dried over $MgSO_4$, and concentrated. Purification was accomplished by radial chromatography on silica gel (elution with 25:1 hexanes−ethyl acetate) to give a mixture of diastereomers as a colorless oil in a 73:27 *cis*/*trans* ratio: yield = 82 mg (0.34 mmol) = 87%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.90−1.51 (m, 7H), 2.07 (m, 2H), 2.63 (s, 0.27H), 2.71 (s, 0.73H), 5.90 (s, 0.73H), 6.21 (s, 0.27H) 7.10−7.25 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (13.9, 14.1), 17.1, 22.9, 31.6, 77.2, (79.5, 80.3), (83.1, 83.7), (90.5, 91.7), (113.3, 113.9), 125.1, 128.4(2), 129.3(2), 134.0, (145.9, 146.2); MS *m*/*z* ($M^+$) calcd 240.0973, obsd 240.0973. Anal. Calcd for $C_{16}H_{16}S$: C, 79.95; H, 6.71. Found: C, 80.09; H, 6.60.




**III.a.2. Formation of 6-Phenylhex-3-ene-1,5-diyne-3-phenyl Sulfide. III.a.2.a. *Anti*-Isomer Only.** A solution of the hydroxy sulfide (200 mg 0.72 mmol) in a 9:1 THF/$H_2O$ mixture (20 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid. The solution was stirred at room temperature for 10−15 h and diluted with 10% sodium bicarbonate solution (aqueous, 20 mL). After 5 min of stirring, 30 mL of dichloromethane was added to the solution with stirring for 10 min. The separated aqueous layer was extracted with 3×10 mL of dichloromethane. The organic layers were combined, washed with 3 × 10 mL of water, dried over $MgSO_4$, and concentrated. Purification was accomplished by radial chromatography on silica gel (elution with 25:1 hexanes−ethyl acetate) to give the product as a colorless oil in a 97:3 *E*/*Z* ratio (the minor isomer was detected by GC−MS; the minor isomer was not seen by NMR): ield = 156 mg (0.60 mmol) = 83%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.2.95 (s, 1H), 6.01 (s, 1H), 7.07−7.30 (m, 10H): $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 81.7, 82.9, 89.3, 92.6, 114.0, 122.0, 125.7, 128.1 (2), 128.3, 128.8 (2), 129.5 (2), 133.6 (2), 134.0, 144.6. Anal. Calcd for $C_{18}H_{12}S$: C, 83.04; H, 4.65. Found: C, 82.91; H, 4.80.

**III.a.2.b. Mixture of Isomers.** A solution of the hydroxy sulfide mixture (20:80 *syn*/*anti*) (200 mg, 0.72 mmol) in a 9:1 THF/$H_2O$ mixture (20 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid. The solution was stirred at room temperature for 10−15 h and diluted with 10% sodium bicarbonate solution (aqueous, 20 mL). After 5 min of stirring, 30 mL of dichloromethane was added to the solution with stirring for 10 min. The separated aqueous layer was extracted with 3×10 mL of dichloromethane. The organic layers were combined, washed with 3 × 10 mL of water, dried over $MgSO_4$, and concentrated. Purification was accomplished by radial chromatography on silica gel (elution with 25:1 hexanes−ethyl acetate) to give a mixture of diastereomers as a colorless oil in a 77:23 *E*/*Z* ratio: yield = 160 mg (0.61 mmol) = 85%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.2.95 (s, 0.77H), 3.01 (s, 0.23H), 6.04 (s, 0.77H), 6.35 (s, 0.27H), 7.07−7.30 (m, 10H): $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (81.5, 81.7), 83.0, 89.3, (92.6, 93.0), (114.0, 119.2), 122.0, 125.7, 128.1 (2), (128.3, 128.5), 128.8 (2), 129.5 (2), 133.6 (2), (134.0, 134.5), (144.6, 145.1).

**III.a.3. Formation of 6-Trimethylsilylhex-3-ene-1,5-diyne-3-phenyl Sulfide. III.a.3.a. *Anti*-Isomer Only.** A solution of the hydroxy sulfide (200 mg 0.73 mmol) in a 9:1 THF/$H_2O$ mixture (20 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid. The solution was stirred at room temperature for 10−15 h and diluted with 10% sodium bicarbonate solution (aqueous, 20 mL). After 5 min of stirring, 30 mL of dichloromethane was added to the solution with stirring for 10 min. The separated aqueous layer was extracted with 3×10 mL of dichloromethane. The organic layers were combined, washed with 3 × 10 mL of water, dried over $MgSO_4$, and concentrated. Purification was accomplished by radial chromatography on silica gel (elution with 15:1 hexanes−ethyl acetate) to give the product as a colorless oil in a 97:3 *E*/*Z* ratio (the minor isomer was detected by GC−MS; the minor isomer was not seen by NMR): yield = 123 mg (0.0.48 mmol) = 65%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.0.11 (s, 9H), 2.87 (s, 1H), 6.20 (s, 1H), 7.10−7.29 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 0.09 (3), 78.7, 81.2, 95.3, 100.9, 112.5, 124.8, 127.2(2), 128.7(2), 131.8, 142.1. Anal. Calcd for $C_{15}H_{16}SSi$: C, 70.25; H, 6.29. Found: C, 69.99; H, 6.43.

**III.a.3.b. Mixture of Isomers.** A solution of the hydroxy sulfide mixture (40:60 *syn*/*anti*) (200 mg 0.73 mmol) in a 9:1 THF/$H_2O$ mixture (20 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid. The solution was stirred at room temperature for 10−15 h and diluted with 10% sodium bicarbonate solution (aqueous, 20 mL). After 5 min of stirring, 30 mL of dichloromethane was added to the solution with stirring for 10 min. The separated aqueous layer was extracted with 3×10 mL of dichloromethane. The organic layers were combined, washed with 3 × 10 mL of water, dried over $MgSO_4$, and concentrated. Purification was accomplished by radial chromatography on silica gel (elution with 15:1 hexanes−ethyl acetate) to give a mixture of diastereomers as a colorless oil in a 50:50 *E*/*Z* ratio: yield = 120 mg (0.48 mmol) = 65%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.09 (s, 4.5H) 0.10 (s, 4.5H) 2.81 (s, 0.5H), 2.87 (s, 0.5H), 5.77 (s, 0.5H), 6.20 (s, 0.5H), 7.10−7.29 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 0.09 (3), (78.7, 79.1), (81.2, 81.8), (95.3, 95.9), 100.9, (112.5, 116.1), 124.8, 127.2(2), 128.7(2), (131.8, 132.9), (142.1, 143.5).

**III.a.4. Formation of 6-(*tert*-Butyldimethylpropoxysilyl)hex-3-ene-1,5-diyne-3-phenyl Sulfide.** A solution of the hydroxy sulfide mixture (15:85 *syn*/*anti*) (250 mg 0.67 mmol) in a 9:1 THF/$H_2O$ mixture (10 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid. The solution was stirred at room temperature for 8−12 h and diluted with 10% sodium bicarbonate solution (aqueous, 10 mL). After 5 min of stirring, 20 mL of dichloromethane was added to the solution with stirring for 10 min. The separated aqueous layer was extracted with 3×10 mL of dichloromethane. The organic layers were combined, washed with 3 × 10 mL of water, dried over $MgSO_4$, and concentrated. Purification was accomplished by radial chromatography on silica gel (elution with 10:1 hexanes−ethyl acetate) to give a mixture of diastereomers as a colorless oil in an 82:18 *cis*/*trans* ratio: yield = 192 mg (0.54 mmol) = 80%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.15 (s, 6H), 0.93 (s, 9H), 1.27 (m, 2H), 2.11(m, 2H), 2.71 (s, 0.82H), 2.80 (s, 0.18H), 3.75 (m, 2H), 5.93 (s, 0.82H), 6.16 (s, 0.18H), 7.07−7.26 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 0.13(2), (13.9, 14.1), (15.0, 15.1), 21.3(3), 33.9, (64.9, 65.3), (77.3, 78.1), (79.7, 80.1), (83.2, 84.1), (93.1, 93.7), (114.1, 115.0), 125.4, 127.7(2), 129.1, 129.3, (133.7, 134.0), (144.9, 145.4); MS *m*/*z* ($M^+$) calcd 356.1630, obsd 355.9891. Anal. Calcd for $C_{21}H_{28}OSSi$: C, 70.73; H, 7.91. Found: C, 70.81; H, 8.01.

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**Supporting Information Available:** $^{1}H$ and $^{13}C$ NMR spectral data are available for each hydroxy sulfide (**2**), epoxydiyne (**5**), and ene diyne (**6**). Spectral data for each isomer are shown where separation of the isomers was possible. This material is available free of charge via the Internet at http://pubs.acs.org.