

SYNTHESIS OF POLYCYCLIC HETEROAROMATIC COMPOUNDS
VIA THE INTRAMOLECULAR [4+2] CYCLOADDITION
OF CONJUGATED HETARENYNES AND ALKYNES

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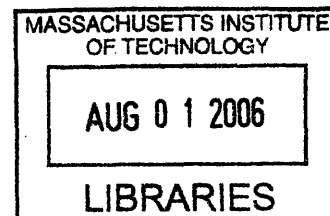
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“As we express our gratitude, we must never forget that the highest appreciation is not to utter words, but to live by them.” John Fitzgerald Kennedy.

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*To Michael and Mami, the two most important people in my life,
and to my babies Helena, Sebastian, Montgomery, Tess, and Sophie
for the many years of joy and companionship.*

Synthesis of Polycyclic Heteroaromatic Compounds via the
Intramolecular [4+2] Cycloaddition of Conjugated Heteroenynes and Alkynes

By

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Requirements for the Degree of Doctor of Philosophy

ABSTRACT

This dissertation describes studies of the feasibility and scope of intramolecular [4+2] cycloadditions of heteroenynes and alkynes as a method for the synthesis of polycyclic benzo[b]-fused five-membered heteroaromatic compounds. Only scattered reports of this transformation existed prior to our work and these were very limited in their scope. The research presented in this thesis demonstrates that the synthesis of benzo[b]-fused five-membered heteroaromatic compounds can be effectively carried out under relatively mild thermal conditions utilizing alkynylpyrroles, -thiophenes, or -furans tethered to alkynes. The heteroenyne cycloaddition substrates are readily prepared in 2-3 steps from commercially available or known 2- or 3-haloheterarenes via Sonogashira coupling followed in most cases by a Mitsunobu reaction. In the majority of cases metalation of a terminal alkyne with a Grignard reagent and then reaction with various electrophilic reagents allows for the creation of a library of cycloaddition substrates.

The scope of the heteroenyne cycloaddition was explored with respect to four major variables in the cycloaddition substrates: (1) the nature of activating groups attached to the alkynyl 2π component; (2) the composition of the tether connecting the 2π and 4π components; (3) the type of heterarene (i.e., pyrrole, thiophene, or furan); and (4) the position of attachment of the tether to the heterarene. The experimental findings can be summarized as follows: (1) electron-withdrawing and electronegative groups attached to the 2π component accelerate the cycloaddition; (2) electronegative heteroatoms within the tether accelerate the cycloaddition; (3) the order of reactivity of heteroenynes is: alkynyl-(*N*-Boc)pyrrole \sim alkynylfuran $>$ alkynylthiophene; and (4) attachment of the tether bearing the 2π component at C-2 of the heterarene leads to a more facile reaction than attachment at C-3. Finally, the cycloaddition of substrates having Lewis basic substituents attached to the 2π component can be effectively promoted by the use of Lewis acids under very mild conditions, leading in most cases to an improved yield.

Thesis Supervisor: Rick L. Danheiser

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Part I:
Introduction and Background

Chapter 1. Synthesis of Benzo-Fused Five-Membered Heterocycles

1.1. Introduction

Five-membered heteroaromatic compounds and their benzo-fused derivatives are ubiquitous in nature and are essential core components in many pharmaceuticals as well as other commercially important compounds.¹ Consequently, the development of more efficient synthetic methods for this class of compounds is important to organic chemists. Cycloadditions are an important family of reactions widely used for the synthesis of carbocyclic and heterocyclic compounds,² and their intramolecular variants are very powerful methods for producing polycyclic ring systems in a single step, a feature that has been greatly exploited in organic synthesis.³

Many of the research efforts in the Danheiser group over the last two decades have focused on the development of methods for the regio- and stereocontrolled synthesis of carbocyclic and heterocyclic rings. The intramolecular enyne cycloaddition strategy largely developed in the Danheiser group exploits the easy assembly of conjugated enynes⁴ and the reactivity of highly-unsaturated conjugated molecules in cycloadditions to yield polycyclic aromatic systems from acyclic precursors in one step.

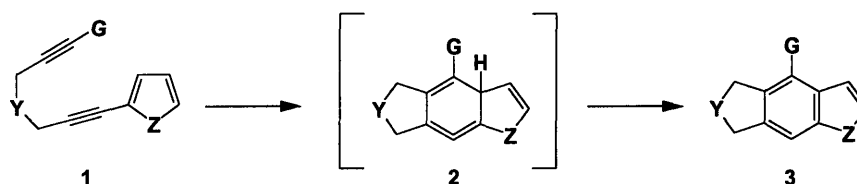
¹ For a comprehensive discussion of the structure, reactivity, synthesis, and applications of benzo-fused five-membered heterocycles see: (a) Thomas, E. J., Ed. *Science of Synthesis*; Georg Thieme Verlag: Stuttgart, Germany, 2001; Vol 10, pp 11-75, 155-181, and 361-624. (b) Bird, C. W., Ed. *Comprehensive Heterocyclic Chemistry II*; Elsevier Science Ltd: Tarrytown, NY, 1996; Vol 2, pp 1-729. (c) Gilchrist, T. *Heterocyclic Chemistry*, 3rd ed.; Prentice Hall: Harlow, England, 1997.

² (a) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990.

³ For example, see reviews on the intramolecular Diels-Alder reaction and its application: (a) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779. (b) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 820. For a review on intramolecular dipolar cycloadditions see: (c) Namboothiri, I. N. N.; Hassner, A. *Topics Curr. Chem.* **2001**, *216*, 1.

⁴ For reviews on methods for preparing conjugated enynes see: (a) Brandsma, L. *Synthesis of Acetylenes, Allenes and Cumulenes: Methods and Techniques*, 1st ed.; Elsevier: Oxford, 2004. (b) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988. (c) Brandsma, L.; Vasilevsky, S. F.; Verkrujisse, H. D. *Application of Transition Metal Catalysis in Organic Synthesis*; Springer: New York, 1998. (d) Diederich, F.; Stang, P. J. *Metal Catalyzed Cross-Coupling Reactions*; Wiley-VCH: New York, 1998. (e) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

Much research in the group has focused on studying the scope, mechanism, and practical synthetic applications of this chemistry.^{5,6} My research was aimed at further expanding the scope of this chemistry by applying it in an efficient method for the synthesis of indoles, benzo[b]furans, and benzo[b]thiophenes. This new approach involves the intramolecular cycloaddition of conjugated alkynyl five-membered heteroarenes (i.e., pyrroles, furans, and thiophenes) as 4π components as depicted below.



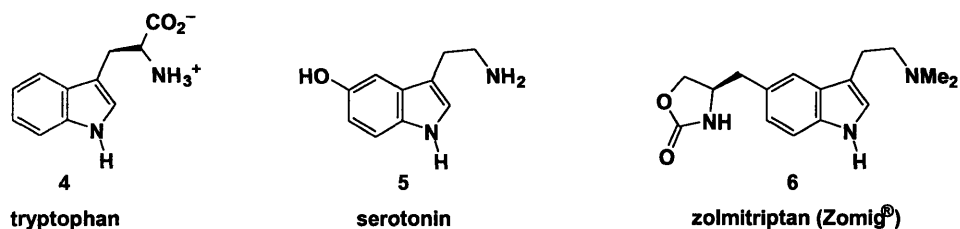
This thesis begins by describing some of the existing methodology for the synthesis of benzo-fused five-membered heterocycles using intramolecular approaches, establishing comparisons where appropriate with the hetarenyne cycloaddition chemistry described in detail in subsequent chapters. A summary of the theoretical and experimental background concerned with enyne and arenyne cycloadditions is then presented, followed by a detailed description of our new hetarenyne cycloaddition chemistry.

⁵ (a) Danheiser, R. L.; Gould, A. E.; Fernandez de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514. (b) Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378. (c) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776. (d) Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3917.

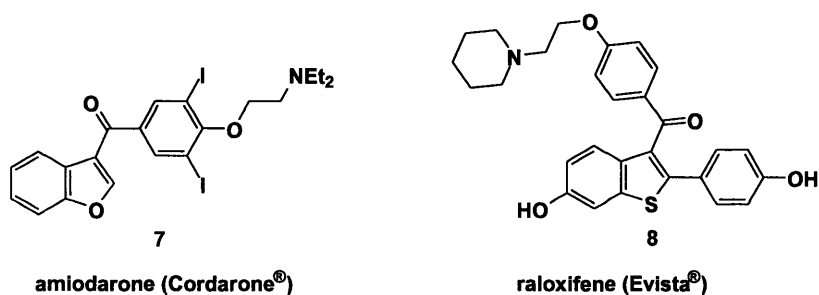
⁶ For a more detailed discussion of the background, scope, and mechanism of the enyne and related cycloadditions see: (a) Dunetz, R. L., Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 2005. (b) Hayes, M. L., Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 2004. (c) Diffendal, J. M., Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, September 2002. (d) Palucki, B. L., Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1997. (e) Gould, A. E., Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1996. (f) Helgason, A. E., Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1994.

1.2. General Importance of Benzo-Fused Five-Membered Heterocycles

Benzo-fused five-membered heterocycles are important structural components of biologically significant natural and synthetic compounds. For example, the indole nucleus^{1,7} is contained in natural molecules like tryptophan (4), an essential amino acid and building block for proteins, and serotonin (5), a neurotransmitter implicated in diseases like depression and anxiety disorders. The indole system is also present in many pharmaceuticals such as zolmitriptan (6), a drug currently on the market for the treatment of migraine headaches.



Benzo[b]furans¹ are less common in nature, but like indoles are present in many pharmaceutical agents, including the widely used antiarrhythmic agent amiodarone (7). Benzo[b]thiophenes are virtually unknown in natural products but are also often found in pharmaceuticals, such as the selective estrogen receptor modulator raloxifene (8) used in the treatment of post-menopausal osteoporosis.

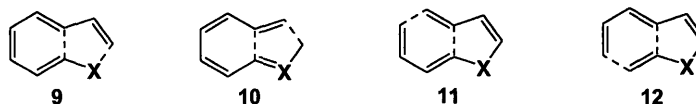


The importance of these heteroaromatic systems makes the development of more efficient methods for their synthesis very desirable in many applications. This section

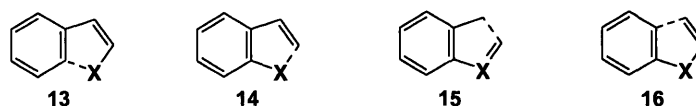
⁷ Sundberg, R. J. *Indoles*; Academic Press, Inc.: San Diego, CA, 1996.

reviews methods for the construction of benzo-fused five-membered heterocycles with a focus on *intramolecular processes*. The methods currently known for the synthesis of these heterocyclic systems involving intramolecular processes can be classified as either annulations or cyclizations, and can be further divided into three categories:

(A) Formation of both rings via intramolecular annulation



(B) Formation of the five-membered ring via a cyclization reaction



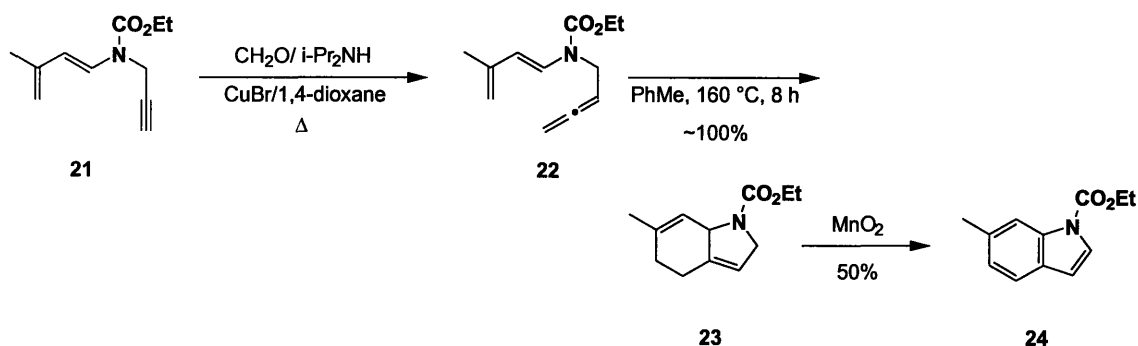
(C) Formation of the six-membered ring via a cyclization reaction



Not all the bond-forming modes depicted above are known and a comprehensive discussion of all the known synthetic methods is beyond the scope of this thesis. Therefore, only selected examples will be presented and compared with the strategy developed as part of the research described in later chapters. The aim is to present a sampling of some of the known synthetic methods that allow for the intramolecular formation of benzo[b]-fused five-membered heteroaromatic compounds within a few steps from readily available building blocks, similarly to our chemistry. Where appropriate, any relevant strategic, tactical, and/or mechanistic comparisons with our chemistry will be made and discussed.

1.3. Generation of Both Rings via Intramolecular Annulation

Intramolecular cycloadditions are especially powerful methods for the construction of polycyclic systems. Only a few examples are known of syntheses of five-membered benzo-fused heteroaromatic rings via intramolecular annulation. The preparation of indole **24** illustrates such a strategy proceeding via mode 11. The synthesis of **24** was accomplished beginning with propargylic dienamine **21** and involved a three step procedure starting with homologation of the alkyne to an allene, followed by an intramolecular Diels-Alder reaction that furnished cycloadduct **23**. Oxidation of this product with MnO_2 yielded indole **24**.⁸



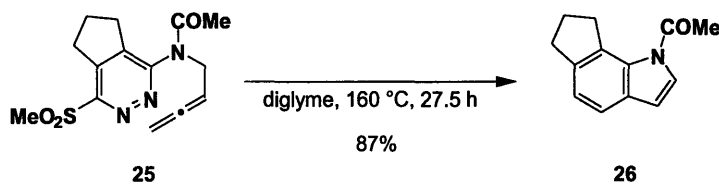
Dienamine **21** was readily prepared from an α,β -unsaturated aldehyde and propargylamine, followed by *N*-carboethoxylation with ethyl chloroformate. By using more highly substituted aldehydes, as well as 2-substituted propargylamines, one could create indoles with multiple substituents in one step, making this an efficient method for the synthesis of highly substituted indoles.

A related method for the synthesis of indoles was reported by Boger which involves the intramolecular [4+2] cycloaddition of aminopyridazine **25** followed by cycloreversion with loss of N_2 , and finally elimination of methanesulfinic acid to produce **26**.⁹ Although this method can also provide highly substituted heteroaromatic rings, the

⁸ Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1986**, *27*, 1837.

⁹ Boger, D. L.; Saky, S. M. *J. Org. Chem.* **1988**, *53*, 1415.

attractiveness of this strategy is somewhat diminished by the effort required to prepare the pyridazine cycloaddition substrates like **25**.

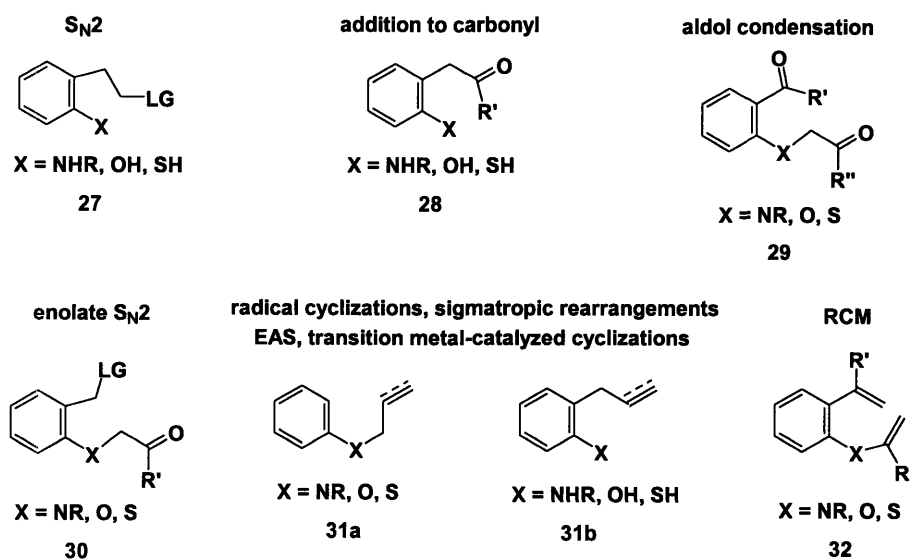


To the best of our knowledge, no examples have been reported in which analogous strategies have been applied to the synthesis of benzo[b]furans or benzo[b]thiophenes. Although these methods are able to produce the bicyclic core of the indole system, they involve the assembly of reactive and somewhat exotic diene components (e.g. substituted pyridazines like **25**). Furthermore, additional steps to oxidize the initial cycloadduct to the fully aromatized indole may be required, as in the case of **23**. Our chemistry, on the other hand, involves the straightforward preparation of simple alkynyl hetarenes and simply requires heat to produce the fully aromatic cycloadduct in one step (*vide infra*).

1.4. Formation of the Five-Membered Ring via a Cyclization Reaction

The most widely used intramolecular processes for the synthesis of benzo-fused five-membered heteroaromatic compounds involve the construction of the five-membered ring onto a pre-existing benzenoid system. Because of the large number of different methods in this category, many with little relevance to the chemistry that will be presented later in this thesis, only a very brief overview will be given here. The reader is directed to the volumes of information contained within other sources for more examples and a detailed discussion.¹

Generally speaking, the methods for the formation of a five-membered ring via cyclization onto a pre-existing benzenoid system involve the following approaches:¹⁰



Although these methods can often generate the desired products very efficiently, preparation of the substrates for the cyclization step can involve multistep serial functionalization sequences. In some cases, tactical problems involving functional group incompatibility can arise in these approaches, which are also intrinsically less convergent than alternative strategies. In particular, the intramolecular cycloaddition strategy developed in our laboratory is more convergent as compared to these cyclization strategies, and also provides much more efficient access to benzo-fused heteroaromatic systems that bear multiple substituents on the benzenoid ring.

1.5. Formation of the Six-Membered Ring via a Cyclization Reaction

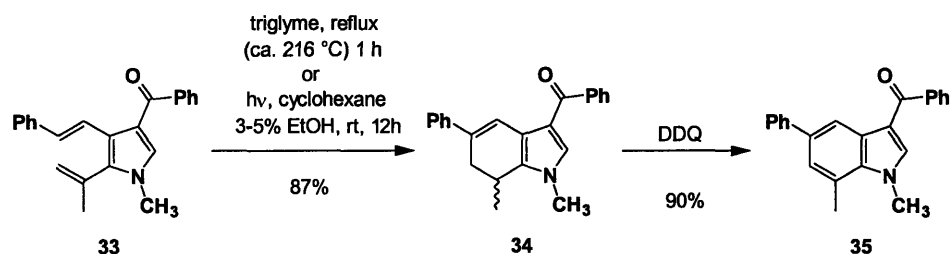
The new method for the synthesis of benzo-fused heteroaromatic compounds presented in this thesis involves the formation of a new six-membered aromatic ring via a

¹⁰ For some examples the application of ring-closing metathesis for the synthesis of benzo-fused five-membered heterocycles see: (a) Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem. Int. Ed. Engl.* **2006**, *46*, 2664, and references cited therein.

cycloaddition reaction of an alkynyl heteroarene. This section will discuss various existing methods for the construction of similar heteroaromatic compounds involving the formation of a new six-membered ring onto a five-membered heteroarene. Given the multitude of examples available, only a select few will be presented here in some detail, establishing comparisons when relevant with strategic, tactical, and/or mechanistic features of our chemistry.

1.5.1. Thermal and Photochemical Electrocyclizations¹¹

In 1986, van Leusen reported the two-step synthesis of indole **35** from divinyl pyrrole **33**.¹² Thermal or photochemical 6π electrocyclization of **33** gave the bicyclic intermediate **34**, which readily yielded the desired indole upon oxidation with DDQ.



The 2,3-divinylpyrrole **33** was prepared via a multistep sequence featuring an application of the van Leusen pyrrole synthesis.¹³ The high temperature required for the 6π electrocyclization and the requirement for an additional dehydrogenation step are not attractive, but the method can also be performed under photochemical conditions. This method was also successfully applied to the synthesis of benzimidazoles and benzoxazoles.¹⁴

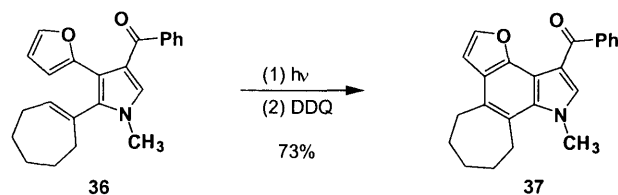
¹¹ For a detailed discussion on electrocyclic reactions see: (a) Ansari, F. L.; Qureshi, R.; Qureshi, M. L. *Electrocyclic Reactions: From Fundamentals to Research*, Wiley-VCH: Hoboken, NJ, 1999. (b) Marvell, E. N. *Thermal Electrocyclic Reactions*, Academic Press, Inc.: San Diego, CA, 1981.

¹² Moskal, J.; van Leusen, A. M. *J. Org. Chem.* **1986**, *51*, 4131.

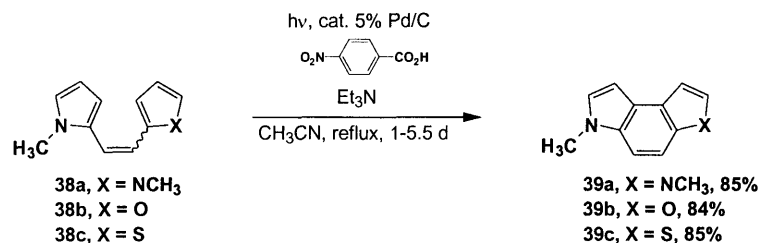
¹³ (a) van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; van Leuden, D. *Tetrahedron Lett.* **1972**, *13*, 5337. (b) van Leusen, D.; Flentge, E.; van Leusen, A. M. *Tetrahedron* **1991**, *47*, 4639.

¹⁴ Moskal, J.; van Stralen, P.; Postma, D.; van Leusen, A. M. *Tetrahedron Lett.* **1986**, *27*, 2173.

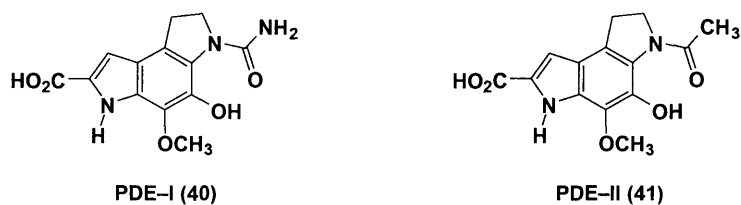
Similar chemistry was also reported with substrates where a heteroarene serves as one of the electrocyclization π components, resulting in a bis-hetaryl-fused benzene ring, as illustrated in the following transformation.¹⁴



A related method was reported by Cava involving the photocyclization and in situ catalytic dehydrogenation of heterostilbenoid compounds.¹⁵ Irradiation of 2-(2-arylviny)pyrroles **38a**, **38b**, and **38c** in the presence of catalytic amounts of 5% Pd/C yielded the corresponding photocyclization products **39a**, **39b**, and **39c** in good yield.

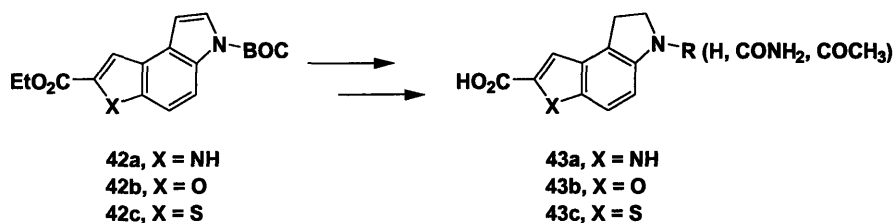


This chemistry was later applied to the synthesis of derivatives **43a**, **43b**, and **43c** of the cAMP phosphodiesterase inhibitors PDE-I (**40**) and PDE-II (**41**) isolated from *Streptomyces zelensis*.¹⁶

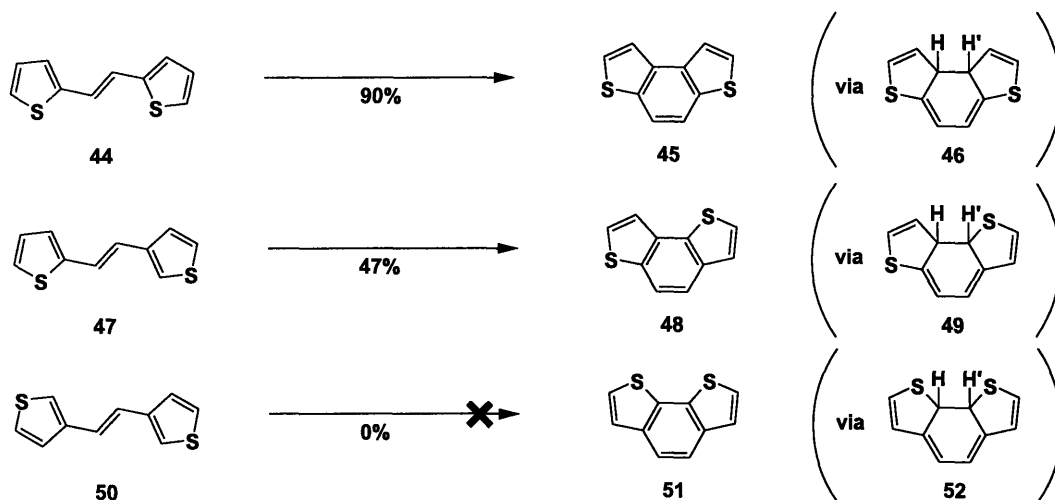


¹⁵ Rawal, V. H.; Jones, R. J.; Cava, M. P. *Tetrahedron Lett.* **1985**, 26, 2423.

¹⁶ Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, 52, 19.



A few years earlier Kellogg was studying the photocyclization of (bis-thienyl)ethenes and noticed the position of attachment of the vinyl group to the heteroarenes had a tremendous impact on the outcome of the reaction,¹⁷ an issue that turned out to have great relevance to our own work (*vide infra*). Kellogg reported that irradiation of bis-(2-thienyl)ethene **44** yields 90% of the desired cyclization product **45**; however, in the case of substrates having either one (**47**) or both (**50**) of the thiophenes attached to the central alkene via position 3, the product yield drops to 47% and 0%, respectively.¹⁸

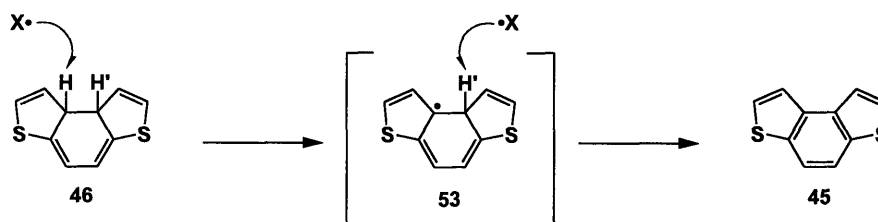


This outcome can be understood by considering the species involved during the oxidation of intermediates **46**, **49**, and **52**. In the case of **46**, abstraction of either hydrogen atom H or H' leads to the same intermediate **53** due to symmetry.

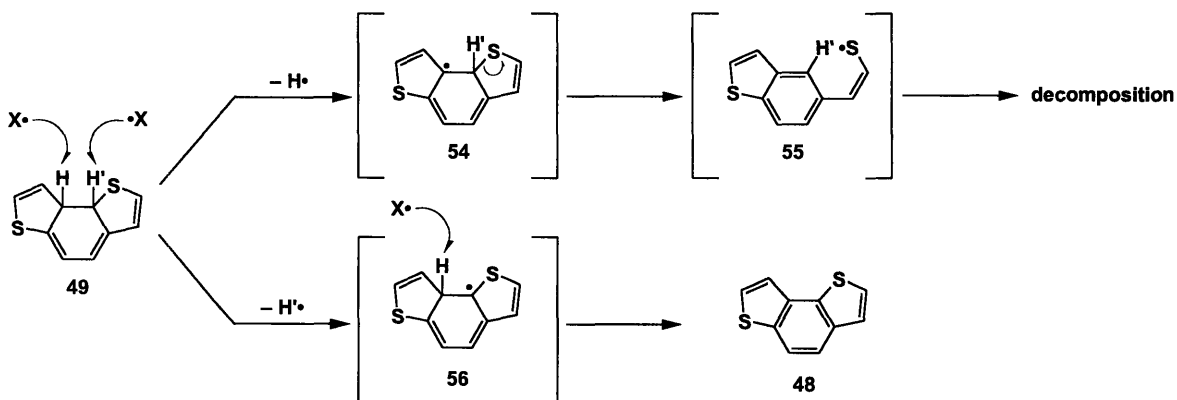
¹⁷ Kellogg, R. M.; Groen, M. B.; Wynberg, H. *J. Org. Chem.* **1967**, *32*, 3093.

¹⁸ Reaction conditions were: hv, 1 mol% I₂, air, benzene (0.01 M), rt, 2-3 h.

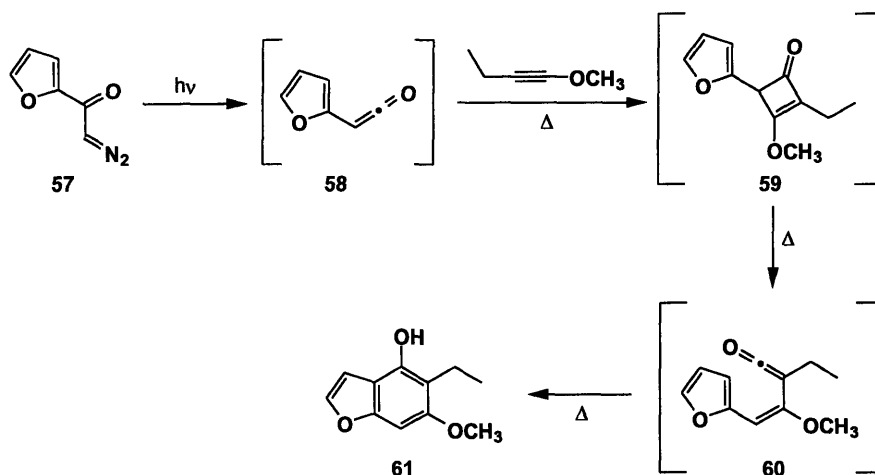
Aromatization of **53** to product **45** then occurs upon abstraction of H' as the only possible reaction pathway, and the desired tricyclic product is obtained in good yield.



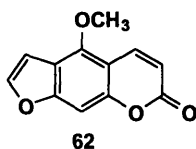
The following analysis explains why the tricyclic products are formed in much lower yield beginning from thiophenes linked via the C-3 position of the ring. In the case of intermediate **49** (resulting from cyclization of **47**), initial abstraction of H or H' results in different intermediates, **54** and **56**, respectively. Radical **56** can aromatize by abstraction of H as discussed above for **53** to afford the tricyclic product **48**. Intermediate **54** can aromatize via abstraction of H' to afford the same tricyclic product **48**. However, fragmentation of **54** can also occur to generate a stable vinylthiyl radical (**55**), which presumably decomposes via various pathways. With **52**, which results from photocyclization of **50** where both thiophenes are linked via their C-3 positions, abstraction of H and H' both lead to the formation of vinylthiyl radicals, and consequently none of the “normal” tricyclic product is obtained.



In 1990, work from our group¹⁹ demonstrated the utility of dienylketene electrocyclizations²⁰ for the synthesis highly substituted indoles, benzo[b]furans, and benzo[b]thiophenes. For example, benzofuran **61** was synthesized utilizing the benzannulation cascade developed in our laboratory, where photochemical Wolff rearrangement of hetaryl diazo ketone **57** in the presence of an alkyne leads to in situ formation of hetarylketene **58** that immediately undergoes a [2+2] cycloaddition with the alkyne, giving the cyclobutenone **59**. This intermediate then undergoes a 4 π electrocyclic ring opening to give (hetaryl)vinylketene **60**, which is followed by a 6 π electrocyclic ring closure resulting in the benzofuran after tautomerization.



This chemistry was subsequently used for the total synthesis of the furocoumarin bergapten (**62**).²¹

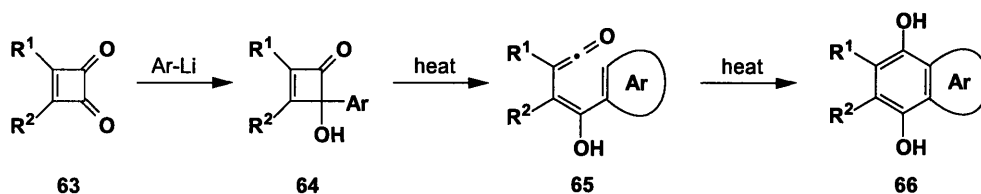


¹⁹ Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.

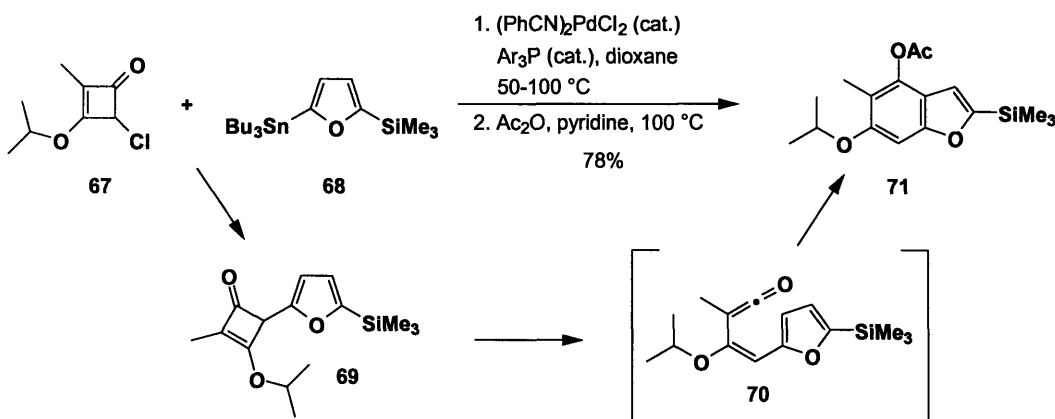
²⁰ For reviews of this and related benzannulation strategies see: (a) Danheiser, R. L.; Dudley, G. B.; Austin, W. F. Product Class 13: Alkenylketenes in *Science of Synthesis*, Danheiser, R. L., Ed., Thieme-Verlag: Stuttgart, Germany, 2006, Vol. 23, pp 522-554. (b) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821.

²¹ Danheiser, R. L.; Trova, M. P. *Synlett* **1995**, 573.

Liebeskind and Moore have independently explored the use of dienylketene cyclizations for the synthesis of aromatic rings, including the application of this chemistry to the synthesis of benzo[b]-fused heterocycles.²⁰ Their main strategy consists of reacting cyclobutene-1,2-diones (**63**) with aryllithium reagents to generate (4-hydroxy-4-aryl)cyclobutenones (**64**). Upon heating, these compounds undergo 4π electrocyclic ring opening yielding (aryl)vinylketenes (**65**) which cyclize in situ via 6π electrocyclic ring closure to furnish the benzo-fused systems (**66**).

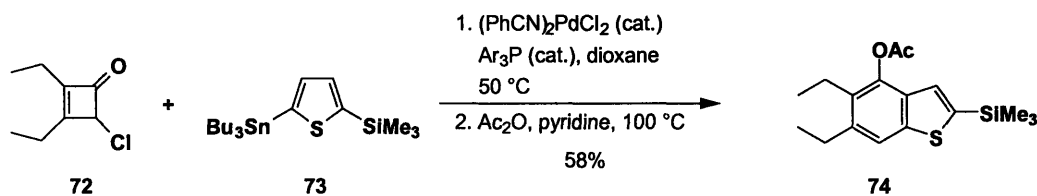


In 1993, Liebeskind reported an alternative method for the preparation of (4-hetaryl)cyclobutenones and their use in the synthesis of benzo[b]furan **71**.²² Thus, Stille coupling of 2-stannylfuran **68** with chlorocyclobutenone **67** gives (2-furyl)cyclobutenone **64**, which undergoes a 4π electrocyclic ring opening as described above to yield the corresponding (2-furyl)vinylketene **70**. The vinylketene then undergoes a 6π electrocyclization to furnish benzo[b]furan **71**.



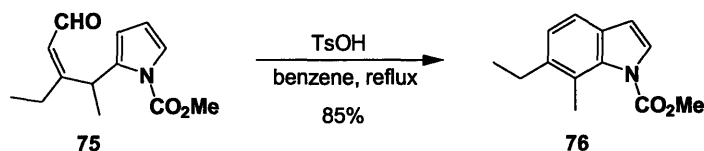
²² Liebeskind, L. S.; Wang, J. J. *Org. Chem.* **1993**, *58*, 3550.

In a similar fashion, the reaction of chlorocyclobutenone **72** with stannylthiophene **73** furnishes the benzo[b]thiophene **74**.



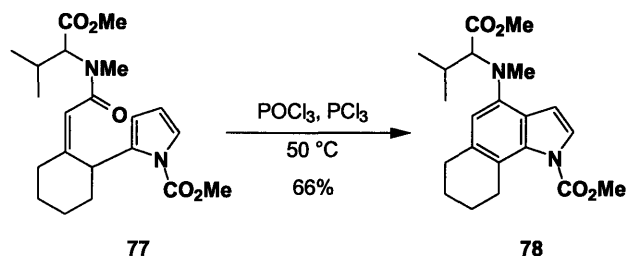
1.5.2. Electrophilic Aromatic Substitution (EAS)

Electrophilic aromatic substitution reactions rank among the most common cyclization methods used for the synthesis of five-membered benzo[b]-fused heteroaromatic systems. Unsaturated carbonyl groups tethered to the heteroarene ring are the most common electrophiles used in these transformations, and catalysis by both protic and Lewis acids has been exploited for cyclizations of this kind. With unsaturated aldehydes and ketones, dehydrating conditions lead to the aromatic system directly, as in the reaction of pyrrolyl aldehyde **75** to give indole **76**.²³ This approach is applicable to substrates with highly substituted side chains, providing access to polysubstituted systems and thereby augmenting the utility of the method.

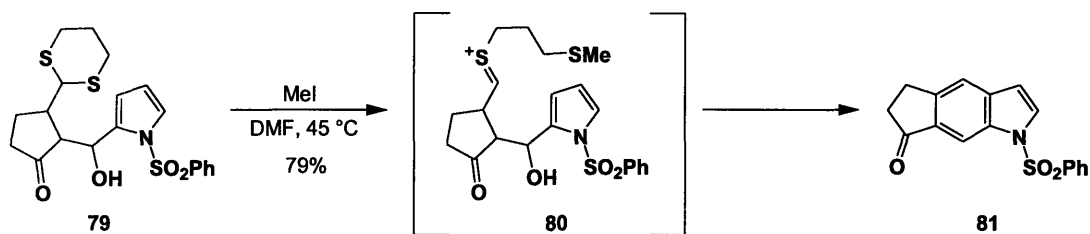


When unsaturated carboxylic acids or amides are used, the resulting benzene rings have hydroxyl, alkoxy, or amino substituents, as illustrated in the cyclization of α,β -unsaturated amido ester **77** to give the aminoindole **78**.²¹

²³ Muratake, H.; Natsume, M. *Heterocycles* **1989**, *29*, 771.

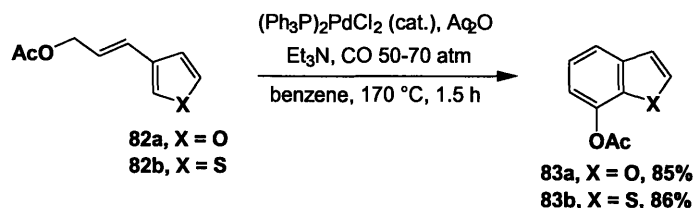


The high nucleophilicity and leaving group ability of sulfur has been exploited to generate thionium ions for electrophilic aromatic substitution reactions. For example, methylation of dithiane **79** leads to ionization followed by nucleophilic attack on carbocation **80** by the pyrrole ring. Sulfide elimination and dehydration then yields the indole **81**.²⁴



1.5.3. Palladium-Catalyzed Cyclizations²⁵

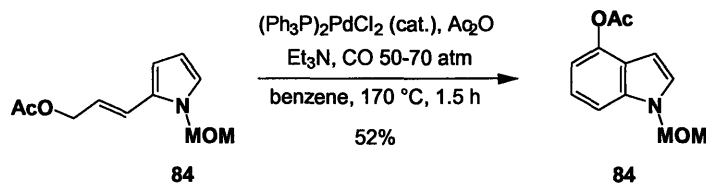
The continuously expanding field of transition metal-catalyzed reactions has proven very useful for the synthesis of indoles and their oxygen and sulfur analogues. Two examples of cyclocarbonylation of (hetaryl)allyl acetates are shown below.²⁶



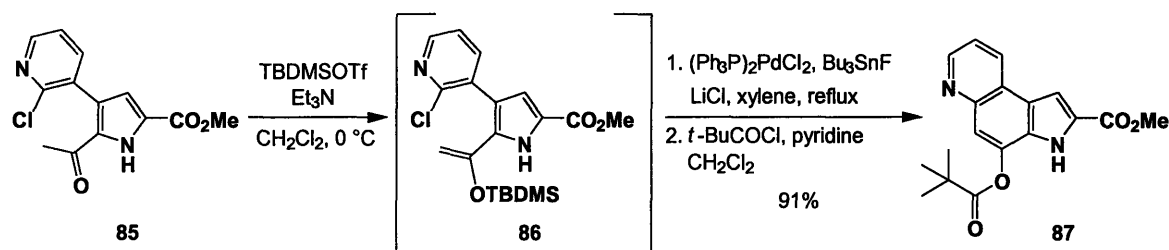
²⁴ Muratake, H.; Natsume, M. *Heterocycles* **1990**, *31*, 683.

²⁵ For reviews of the applications of transition metal-catalyzed cyclizations in the synthesis of heterocyclic compounds see: (a) Negishi, E.-I.; Coperet, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (b) Yamamoto, Y.; Nakamura, I. *Chem. Rev.* **2004**, *104*, 2127. (c) Larock, R. C.; Zeni, G. *Chem. Rev.* **2004**, *104*, 2285. (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.

²⁶ (a) Iwasaki, M.; Li, J.; Kobayashi, Y.; Matsuzaka, H.; Ishii, Y.; Hidai, M. *Tetrahedron Lett.* **1989**, *30*, 95. (b) Iwasaki, M.; Kobayashi, Y.; Li, J.; Matsuzaka, H.; Ishii, Y.; Hidai, M. *J. Org. Chem.* **1991**, *56*, 1922.



In the following example, generation of silyl enol ether **86** from acetyl pyrrole **85** allows for the intramolecular Heck coupling with the 3-(2-chloropyridyl) substituent, furnishing indole **87** in excellent yield.²⁷



The broad functional group tolerability and continuously evolving efficacy and diversity of these types of transformations make them very attractive and powerful methods for the synthesis of heterocycles.

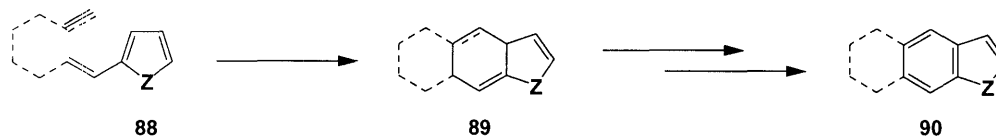
1.5.4. Intramolecular Vinylhetarene Cycloadditions

Although intermolecular [4+2] cycloadditions of vinylhetarenes with alkynes are well known to generate the corresponding five-membered benzo[b]-fused products,²⁸

²⁷ Muratake, H.; Tonegawa, M.; Natsume, M. *Chem. Pharm. Bull.* **1998**, *46*, 400.

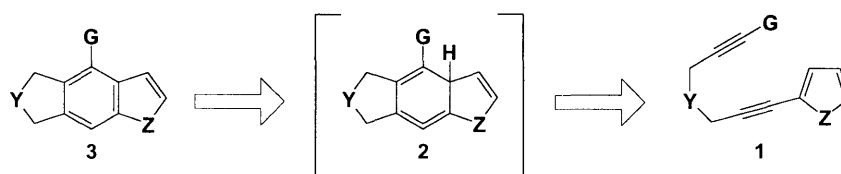
²⁸ For examples see (a) Drew, M. G. B.; Jahans, A.; Harwood, L. M.; Apoux, S. A. B. H. *Eur. J. Org. Chem.* **2002**, *21*, 3589. (b) Yoshida, T.; Ito, A.; Ibusuki, K.; Murase, M.; Kotani, E. *Chem. Pharm. Bull.* **2001**, *49*, 1198. (c) Murase, M.; Yoshida, S.; Hosaka, T.; Tobinaga, S. *Chem. Pharm. Bull.* **1991**, *39*, 489. (d) Ohno, M.; Shimizu, S.; Eguchi, S. *Heterocycles* **1991**, *32*, 1199. (e) Keil, J. M.; Kämpchen, T.; Seitz, G. *Tetrahedron Lett.* **1990**, *31*, 4581. (f) Kusurkar, R. S.; Bhosale, D. K. *Synth. Commun.* **1990**, *20*, 101. (g) Lee, C. K.; Ahn, Y. M. *J. Heterocycl. Chem.* **1989**, *26*, 397. (h) González-Rosende, E.; Jones, R. A.; Sepúlveda-Arquez, J.; Zaballos-García, E. *Synth. Commun.* **1988**, *18*, 1669. (i) Muchowski, J. M.; Scheller, M. E. *Tetrahedron Lett.* **1987**, *28*, 3453. (j) Jones, R. A.; Saliente, T. A.; Arques, J. S. *J. Chem. Soc., Perkin Trans. 1* **1984**, *1*, 2541. (k) Noland, W. E. *J. Org. Chem.* **1983**, *48*, 2488. (l) Jones, R. A.; Marriott, M. T. P.; Rosenthal, W. P.; Arques, J. S. *J. Org. Chem.* **1980**, *45*, 4515. (m) Noland, W. E.; Kim, K. J.; Lee, C. K.; Bae, S. K.; Hahn, C. S. *J. Org. Chem.* **1980**, *45*, 4582. (n) Hosmane, R. S.; Hiremath, S. P.; Schneller, S. W. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2450.

few intramolecular examples exist.²⁹ These methods greatly resemble the hetarenyne chemistry we have developed and will be discussed in some detail in a subsequent chapter. The scarcity of examples of intramolecular versions of these reactions merits further development and reveals that their potential has not been fully exploited.

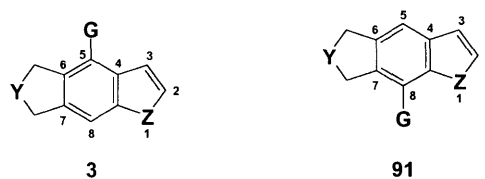


1.5.5. Overview of Hetarenyne Cycloadditions

The hetarenyne method we have developed is based on the following general strategy:



This chemistry allows for the synthesis of five-membered benzo[b]-fused hetarenes specifically functionalized on positions 5, 6, and 7 or 6, 7, and 8, depending on whether the tether is attached to position 2 or 3 of the hetarene in the cycloaddition substrate, as depicted below:



Functional group diversification can be easily achieved depending on the nature of heteroatoms in the tether and the former 2π activating group G. For example, if Y = S, desulfurization can be accomplished with Raney nickel, whereas oxidation to the sulfone

²⁹ For a low-yielding but interesting example using a vinylfuran tethered to an alkyne see: Hayakawa, K.; Yodo, M.; Ohsuki, S.; Kanematsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 6735.

or sulfoxide allows for subsequent alkylation at the benzylic carbons. If $G = \text{SiR}_3$, Hiyama coupling or exchange of the silane for a halogen for other transition metal-catalyzed coupling reactions is possible. With $G = \text{CHO}$ or CO_2R , diversification can be accomplished by oxidation, reduction, olefination, and/or other transformations. Thus, our method allows for the creation of readily functionalizable five-membered benzo[b]-fused nuclei.

The next chapter will present a summary of the enyne, arenynes, and hetarenyne cycloaddition chemistry that is the precedent for the method to be described in detail in subsequent chapters.

Chapter 2. Enyne, Arenyne, and Hetarenyne Cycloadditions

2.1. Introduction

This chapter summarizes background chemistry relevant to the hetarenyne cycloadditions that are the subject of this dissertation. A brief discussion of cycloaromatizations is presented first, illustrating how some of these processes served as the inspiration for the enyne cycloaddition chemistry developed in the Danheiser group. This discussion is followed by a short summary of the chemistry of cyclic allenes that is relevant to enyne and related cycloadditions. Finally, a short review is presented on some of the studies to date on enyne and related cycloaddition reactions.

2.2. Cycloaromatizations

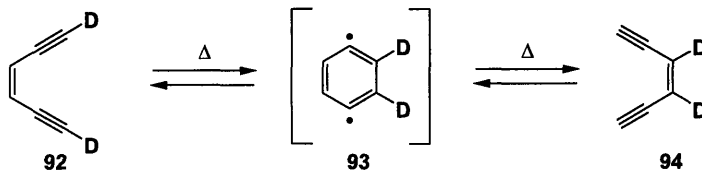
Cycloaromatizations are a family of chemical reactions in which highly unsaturated conjugated molecules undergo cyclization to produce an aromatic biradical.³⁰ Although products resulting from such processes had been previously reported by Sondheimer³¹ and Masamune,³² no mechanistic explanation was provided until Bergman studied the isomerization shown below of the doubly terminally-deuterated conjugated enediyne **92** in the gas phase.³³

³⁰ For reviews on cycloaromatizations see: (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387. (b) Gleiter, R.; Krantz, D. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 842. (c) Grissom, J. W.; Gunawardena, G. U.; Klingsberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453. (d) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (e) *Enediyne Antibiotics as Antitumor Agents*; Borders, D. B.; Doyle, T. W., Eds.; Marcel Dekker: New York, 1995. (f) Nicolaou, K. C.; Smith A. L. In *Modern Acetylene Chemistry* Stang, P. J.; Diederich, F. Eds.; VCH: Weinheim, 1995; pp 203-253. (g) *Neocarzinostatin: The Past, Present, and Future of an Anticancer Drug*; Maeda, H.; Edo, K.; Ishida, N., Eds.; Springer: New York, 1997. (n) Perri, S.T.; Foland, L.D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3068. (o) Sullivan, R. W.; Coghlan, V. M.; Munk, S. A.; Reed, M. W.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 2276.

³¹ Mayer, J.; Sondheimer, F. *J. Am. Chem. Soc.* **1966**, *88*, 603.

³² Darby, N.; Kim, C. U.; Salaiin, J. A.; Shelton, K. W.; Takada, S.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1971**, 1516.

³³ Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 1267.



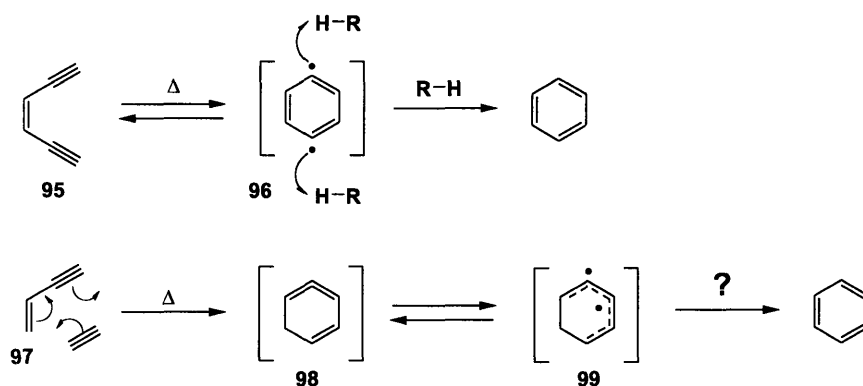
Although cycloaromatizations have been used to synthesize interesting molecular structures including steroid skeletons³⁴ and heterocyclic systems,³⁵ the scope and applicability of these processes in organic synthesis is rather limited. Cycloaromatizations often proceed in low yield and involve the formation of multiple byproducts, which is not surprising as they proceed via the generation of highly reactive biradical species. These reactions proceed with high efficiency only in cases where rapid intramolecular trapping of the biradical can occur, which imposes constraints on the nature of the functionality that can be present in molecules that effectively undergo the transformation.

The Bergman cyclization can be regarded as the 6π electrocyclic ring closure of an enediyne of the type **95** resulting in biradical **96**, which ultimately yields an aromatic product upon abstraction of a hydrogen atom from suitable donors. Consider the electrocyclic ring closure of 1,3,5-hexatriene and the Diels-Alder cycloaddition. Both of these processes involve six π electrons in a pericyclic process that generates a six-membered ring. The same relationship can be envisioned between the Bergman cyclization and the cycloaddition of a conjugated enyne **97** and an alkyne. The resulting cycloadduct, either 1,2,4-cyclohexatriene (**98**) (i.e., isobenzene) or the isomeric biradical **99**, simply requires the migration of a hydrogen atom to then become an

³⁴ Andemichael, Y. W.; Huang, Y.; Wang, K. K. *J. Org. Chem.* **1993**, *58*, 1651.

³⁵ For more examples see (a) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1992**, *114*, 5859. (b) Kim, C.; Russell, K. C. *J. Org. Chem.* **1998**, *63*, 8229. (c) Lu, X. L.; Petersen, J. L.; Wang, K. K. *Org. Lett.* **2003**, *5*, 3277. (d) Li, H.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2003**, *68*, 5512. (e) Li, H.; Yang H.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2004**, *69*, 4500. (f) Majumdar, K.C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2005**, *61*, 10603.

aromatic product. Thus, an alternative strategy for the production of highly unsaturated six-membered rings via a Diels-Alder-type cycloaddition rather than a cyclization was conceived involving highly unsaturated acyclic starting materials. Annulations are inherently more convergent than cyclizations, and it was felt that this type of cycloaddition might potentially provide a much more useful strategy for the formation of six-membered rings than the Bergman cyclization.



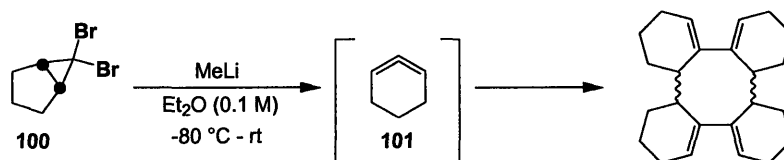
The next section of this chapter reviews the chemistry of cyclic allenes, which are intermediates in the cycloaddition processes described above. This section is followed by a review of the previous literature on enyne and related cycloadditions, as well as examples of the chemistry reported in the years since the initial publication from our laboratory in this area.

2.3. Cyclic Allenes

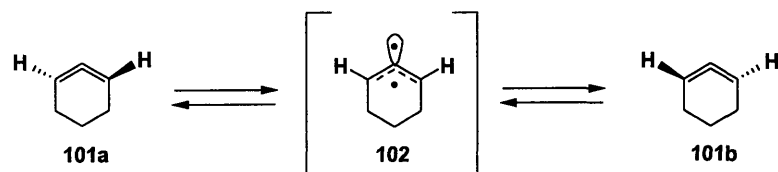
The first comprehensive theoretical study of the structure and stability of strained cyclic allenes was published by Dillon and Underwood in 1974.³⁶ This computational study predicted that the largest ring that can accommodate an allene without distortion is a nine-membered ring. Cyclic allenes of less than nine carbons are expected to be distorted from the normal linear allene geometry.

³⁶ Dillon, P. W.; Underwood, G. R. *J. Am. Chem. Soc.* **1974**, *96*, 779.

Although 1,2-cyclohexadiene (**101**) cannot be isolated, this allene has been synthesized by various routes and trapped in situ, the best approach considered to be the ring opening of dibromocyclopropane **100** reported by Moore and Moser.³⁷



Early experimental and computational studies of 1,2-cyclohexadiene (**101**) by Bottini³⁸ and Balci³⁹ predicted this allene to be chiral, although it can rapidly racemize via biradical intermediate **102**. Subsequent high level *ab initio* calculations performed by Johnson agree that the enantiomeric allenes **101a** and **101b** are the lowest energy structures of 1,2-cyclohexadiene, and that their interconversion occurs via **102**.⁴⁰



In 1992, Janoscheck published a computational study of 1,2,4-cyclohexatriene (“isobenzene”, **98**).⁴¹ The lowest energy structure for **98** was found to be the chiral allene, but it was designated as a “dynamically chiral” structure due to a low racemization barrier. This study concluded that biradicals **99** and **102** are the intermediates in the racemization of the allenes **98** and **101**, respectively.

³⁷ For examples of the utilization of this method see: (a) Moore, W. R.; Moser, W. *J. Am. Chem. Soc.* **1970**, *92*, 5469. (b) Moore, W. R.; Moser, W. *J. Org. Chem.* **1970**, *35*, 908. (c) Bottini, A. T.; Hilton, L. L.; Plott, J. *Tetrahedron* **1975**, *31*, 1997. (d) Shakespeare, W. C.; Johnson, R. P. *J. Am. Chem. Soc.* **1990**, *112*, 8578. (e) Wentrup, C.; Gross, G.; Maquestiau, A.; Flammery, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *27*, 542. (f) Sütbeyaz, Y.; Ceylan, M.; Secen, H. *J. Chem. Research (S)* **1993**, 293.

³⁸ (a) Bottini, A. T.; Corson, F. P.; Fitzgerald, R.; Frost, K. A. *Tetrahedron* **1972**, *28*, 4883. (b) Bottini, A. T.; Hilton, L. L.; Plott, J. *Tetrahedron* **1975**, *31*, 1997.

³⁹ Balci, M.; Jones, W. M. *J. Am. Chem. Soc.* **1980**, *102*, 7607.

⁴⁰ (a) Schmidt, M. W.; Angus, Jr., R. O.; Johnson, R. P. *J. Am. Chem. Soc.* **1982**, *104*, 6838. For a review see: (b) Johnson, R. P. *Chem Rev.* **1989**, *89*, 1111.

⁴¹ Janoscheck, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 476.

In 2001, Engels and Christl published a more detailed high-level computational study on the geometric and electronic structure of 1,2-cyclohexadiene (**101**) and isobenzene (**98**), as well as some aza and oxa heterocyclic variants.⁴² This study confirmed that the strained cyclic allene is the lowest energy structure in all cases and determined that the biradicals **99** and **102** correspond to the *transition states* for the racemization of the allenes.

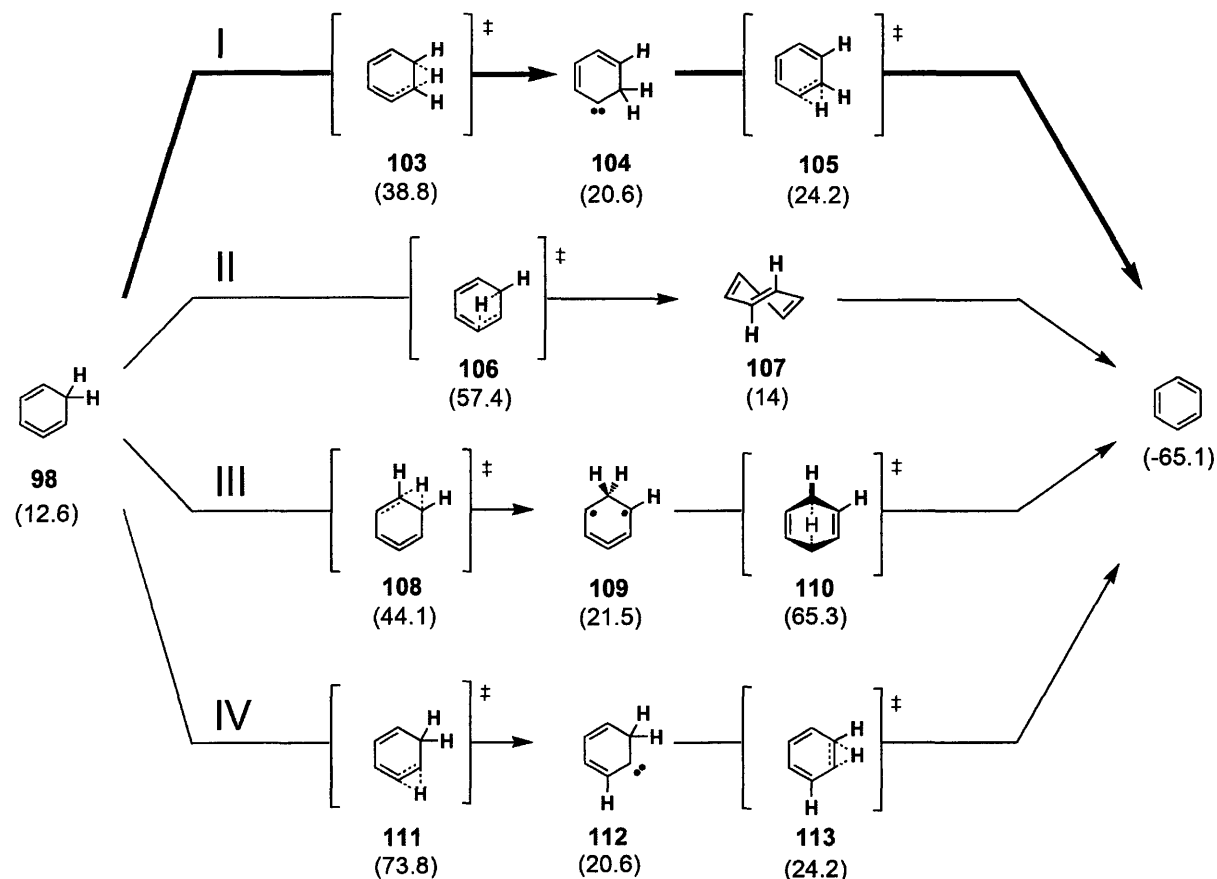
Various intramolecular pathways have been proposed for the isobenzene to benzene isomerization pathway and their relative energies compared using *ab initio* calculations. The following scheme presents a summary of the several pathways considered in these studies by Hopf and Saá.⁴³ In pathway I, a hydrogen atom is transferred from the methylene carbon of **98** via a [1,6]-sigmatropic rearrangement to give carbene **104**, which can then insert into one of the C–H bonds on the adjacent saturated carbon to form the aromatic product. Pathway II represents a [1,5] sigmatropic rearrangement that would transfer a hydrogen atom directly from the methylene of **98** to the central carbon of the cyclic allene. The resulting product would not be benzene, but rather *cis,cis,trans*-1,3,5-cyclohexatriene (**107**), a highly strained and unstable isomer of benzene also known as Möbius benzene.⁴⁴ The high strain of this intermediate is rapidly alleviated by an isomerization that seems to have a negligible energy barrier. Although this mechanism allows for transfer of a hydrogen atom directly to the allene, the high energy of the transition state makes it unlikely. Not only are

⁴² Engels, B.; Schöneboom, J. C.; Münster, A. F.; Groetsch, S.; Christl, M. *J. Am. Chem. Soc.* **2002**, *124*, 287.

⁴³ Numbers in parentheses are free energies in kcal/mol relative to hex-1,3-dien-5-yne. (a) Prall, M.; Krüger, A.; Screiner, P. R.; Hopf, H. *Chem. Eur. J.* **2001**, *7*, 4386. (b) Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Am. Chem. Soc.* **2001**, *123*, 9178. (c) Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Org. Chem.* **2003**, *68*, 1938.

⁴⁴ Johnson, R. P.; Daoust, K. J. *J. Am. Chem. Soc.* **1996**, 7381.

[1,5]-sigmatropic rearrangements in six-membered rings rare,⁴⁵ but the calculated activation energy of pathway **II** (44.8 kcal/mol) is significantly higher than that of pathway **I** (26.2 kcal/mol).



Two alternate pathways (**III** and **IV**) were considered by Hopf^{43a} and Saá^{43b,c} in these computational studies, however, both have such high activation energies when compared with pathways **I** and **II**, that they were discarded as being energetically prohibitive. Therefore, the conclusion is that pathway **I** is the energetically most favorable *intramolecular* isomerization pathway, but the existence of alternate lower energy *bimolecular* isomerization processes cannot be discounted. Hopf notes that the energies calculated for pathway **I** (beginning from the acyclic hex-1,3-dien-5-yne) are

⁴⁵ For recent theoretical discussions of [1,5] sigmatropic rearrangements in 1,3-cyclohexadiene derivatives, see: (a) Hess, B. A., Jr.; Baldwin, J. E. *J. Org. Chem.* **2002**, *67*, 6025. (b) Alabugin, I. V.; Manoharran, M.; Breiner, B.; Lewis, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 9329.

too high to allow for the formation of the aromatic product at the temperatures at which these isomerizations are known to occur (< 200 °C). Hopf speculates that alternate pathways for isomerization could be operating under normal reaction conditions that are favored over the intramolecular route.

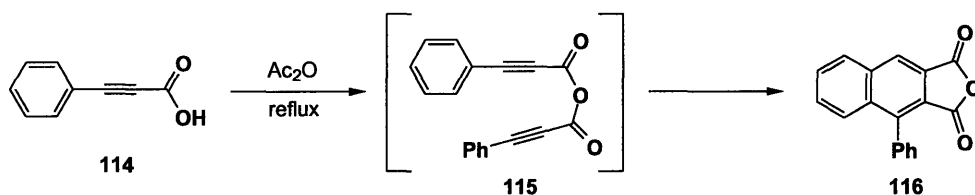
The studies described in this section relate to the structure and reactivity of isobenzenes and other six-membered cyclic allenes generated via electrocyclization, however, they do not address the issue of the feasibility of generating these species using cycloadditions. The next section describes much of the previous work on enyne and related cycloadditions that involve these reactive species.

2.4. Cycloadditions Involving Arenynes and Enynes

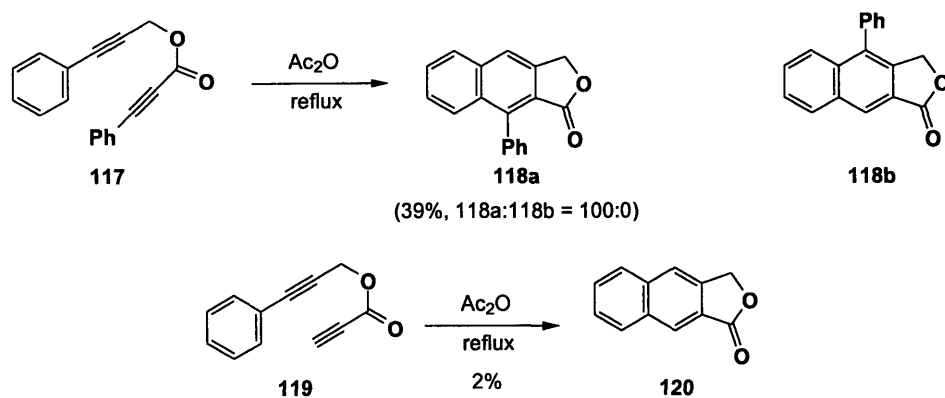
A transformation that is believed to represent an early example of an enyne-type cycloaddition was reported in the late nineteenth century by Michael and Bucher.⁴⁶ They reported the isolation of naphthalene **116** in the attempted synthesis of anhydride **115** from phenylpropionic acid (**114**) in refluxing acetic anhydride. The mechanism of this transformation was not understood at the time, but as shown below, has been suggested by our group to involve a [4+2] cycloaddition of an “arenynne”, i.e., an enyne in which the double bond is embedded within an aromatic ring.^{5a} A few decades later, Baddar explored the scope of this reaction in more detail, showing the reaction proceeds via the initial formation of the anhydride **115**, which under the reaction conditions is converted to the tricyclic product **116**.⁴⁷

⁴⁶ (a) Michael, A.; Bucher, J. E. *Chem. Ber.* **1895**, *28*, 2511. (b) Michael, A.; Bucher, J. E. *Am. Chem. J.* **1898**, *20*, 89.

⁴⁷ (a) Baddar, F. G. *J. Chem. Soc.* **1947**, 224. (b) Baddar, F. G.; El-Assal, L. S. *J. Chem. Soc.* **1948**, 1267. (c) Baddar, F. G.; El-Assal, L. S. *J. Chem. Soc.* **1951**, 1844. (d) Baddar, F. G.; El-Assal, L. S.; Doss, N.A. *J. Chem. Soc.* **1955**, 461. (e) Baddar, F. G.; Fahim, H. A.; Galaby, M. A. *J. Chem. Soc.* **1955**, 465. (f) Baddar, F. G.; El-Assal, L. S.; Doss, N.A. *J. Chem. Soc.* **1959**, 1027. (g) Baddar, F. G.; Moussa, G. E. M.; Omar, M. T. *J. Chem. Soc. (C)* **1968**, 110.



Sixty years after the discovery of the cyclization of anhydride **115**, Klemm explored the cyclization of propargylic *esters* of phenylpropionic acid under Michael-Bucher-like conditions. In 1966, Klemm reported that heating propargylic ester **117** in acetic anhydride gives lactone **118a** selectively, with no formation of regioisomer **118b**.⁴⁸ A follow-up study using ester **119**, which bears a terminal alkyne as the 2π component, yielded very little of the product **120**. These experiments suggest that in these processes, (a) electron rich 4π components are more reactive than electron deficient 4π components, (b) electron deficient 2π components are less reactive than electron rich 2π components, and (c) terminal alkynes are poor substrates for the reaction.⁴⁹



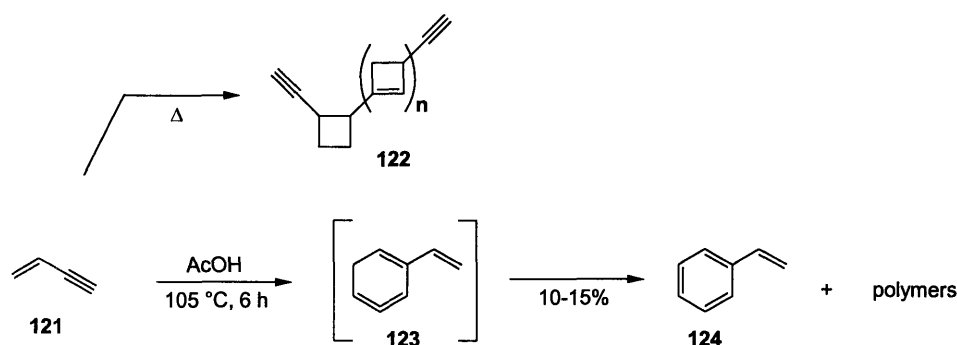
Various other studies of the scope of the Michael-Bucher reaction appeared during the twentieth century,⁵⁰ and the reaction has been used in the synthesis of a variety of compounds, including several natural products.⁵¹

⁴⁸ Klemm, L. H.; Hsu Lee, D.; Gopinath, K. W.; Klopfenstein, C. E. *J. Org. Chem.* **1966**, *31*, 2376.

⁴⁹ Klemm, L. H.; Klemm, R. A.; Santhanam, P. A.; White, D. V. *J. Org. Chem.* **1971**, *36*, 2169.

⁵⁰ (a) Vartanyan, S. A. *Russ. Chem. Rev.* **1962**, *31*, 529. (b) Campbell, A. D.; Grimmett, M. R. *Aust. J. Chem.* **1963**, *16*, 854. (c) Brown, D.; Stevenson, R. *Tetrahedron Lett.* **1964**, *5*, 3213. (d) Maclean, I.; Stevenson, R.

The reactions discussed above involve “arenynes” as the 4π components in what can formally be considered as [4+2] cycloadditions. The first report of an analogous [4+2] cycloaddition involving a non-aromatic conjugated enyne appeared in 1934 when Dykstra isolated styrene (**124**) in low yield while studying the Brønsted acid-catalyzed polymerization of vinylacetylene.⁵² This was the first indication that protic acids might function to promote enyne-type cycloadditions. Dykstra was also the first to mention the possibility of an initial Diels-Alder-type reaction resulting in a cyclic allene intermediate (**123**) that would then isomerize to the aromatic product via an undefined mechanism. However, he concluded an alternate concerted pathway to styrene most likely was operating because of the high strain associated with the cyclic allene. Interestingly, when the reaction was performed in the absence of acid, Dykstra proposed that polymers of the type **122** are obtained.



Various reports of the use of related reactions in the synthesis of interesting compounds began to appear soon thereafter,⁵³ including studies of the stereochemistry of

Chem. Ind. **1965**, 1379. (e) Maclean, I.; Stevenson, R. *J. Chem. Soc. (C)* **1966**, 1717. (f) Brown, D.; Stevenson, R. *J. Org. Chem.* **1965**, *30*, 1759. (g) Holmes, T. L.; Stevenson, R. *J. Chem. Soc. (C)* **1971**, 2091. (h) Cadby, P. A.; Hearn, M. T. W.; Ward, A. D. *Aust. J. Chem.* **1973**, *26*, 557. (i) Stevenson, R.; Weber, J. V. *J. Nat. Prod.* **1989**, *52*, 367.

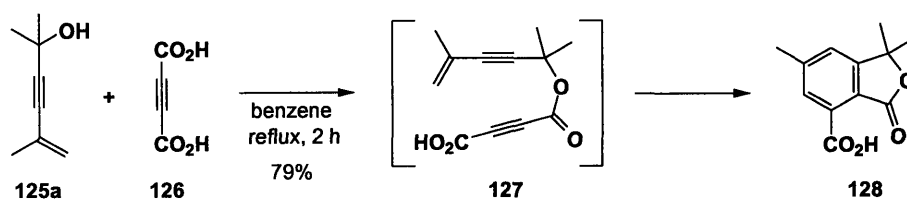
⁵¹ For examples see (a) Hawthorn, R. D.; Kelly, W. *J. Chem. Soc.* **1936**, 745. (b) Baddar, F. G.; El-Assal, L. S. *J. Chem. Soc.* **1951**, 1844. (c) Maclean, I.; Stevenson, R. *Chem. Ind.* **1965**, 1379.

⁵² Dykstra, H. B. *J. Am. Chem. Soc.* **1934**, *56*, 1625.

⁵³ (a) Dane, E.; Höss, O.; Bindseil, A. W.; Schmitt, J. *Ann. Chem.* **1937**, *532*, 39. (b) Dane, E.; Höss, O.; Eder, K.; Schmitt, J.; Schön, O. *Ann. Chem.* **1938**, *536*, 183. (c) Butz, L. W.; Gaddis, A. M.; Butz, E. W. J.; Davis, R. E. *J. Org. Chem.* **1940**, *5*, 379. (d) Butz, L. W.; Gaddis, A. M.; Butz, E. W. J.; Davis, R. E. *J. Am. Chem.*

these transformations that led to the suggestion of a possible mechanistic relationship with the Diels-Alder reaction.

In 1945, A. W. Johnson reported⁵⁴ that the intermolecular reaction of acetylene dicarboxylic acid (126) does not occur with an enyne previously used successfully with maleic anhydride in a similar cycloaddition. Johnson concluded that alkynes are not as reactive as alkenes in these intermolecular Diels-Alder-type reactions. However, in the same study he reported a good yield of phthalide 128 from the reaction of propargylic alcohol 125a with acetylene dicarboxylic acid. Johnson proposed that this reaction proceeds via intermediate 127 resulting from the esterification of propargylic alcohol 125a with acetylenedicarboxylic acid, but he did not speculate on exactly how this intermediate is converted to the final aromatic product.



In 1941, while trying to synthesize ethers of general structure 130 via the acid-catalyzed dimerization of propargylic enynols 129, Nazarov observed the spontaneous cyclization of the desired ethers under the conditions of the reaction.⁵⁵ Nazarov proposed that this reaction proceeds via an intramolecular [4+2] Diels-Alder-type cycloaddition involving vinyl cation intermediate 131,⁵⁶ which results from the non-thermodynamic protonation of 130 at C-3. Elimination of the resulting cyclohexadienyl

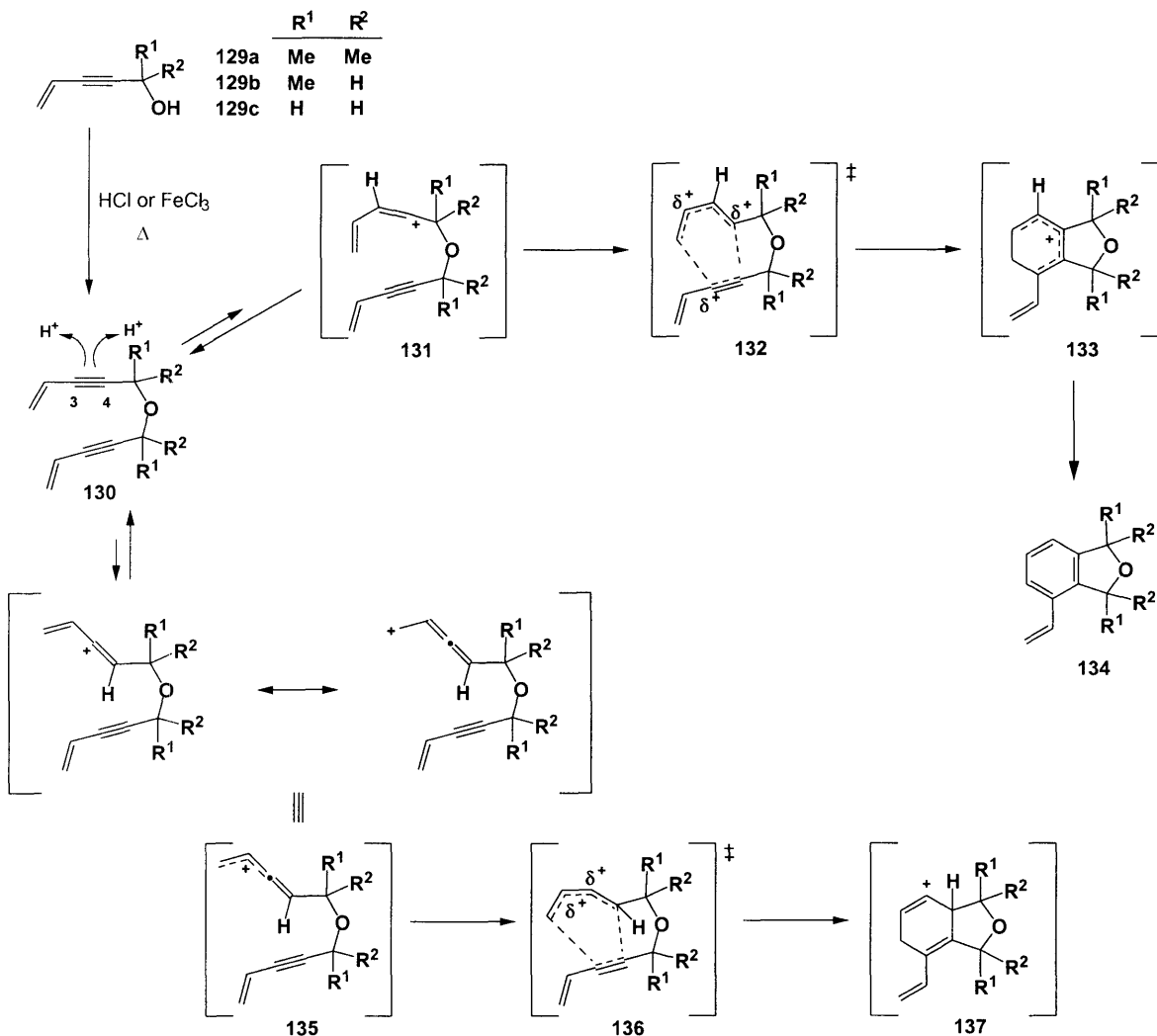
Soc. **1940**, *62*, 995. (e) Butz, L. W.; Joshel, L. M. *J. Am. Chem. Soc.* **1941**, *63*, 3344. (f) Butz, L. W.; Joshel, L. M. *J. Am. Chem. Soc.* **1942**, *64*, 1311.

⁵⁴ Johnson, A. W. *J. Chem. Soc.* **1945**, 715.

⁵⁵ Nazarov, I. N.; Verkholetova, G. P. *Bull. Acad. USSR, Div. Chem. Sci. (Engl. Transl.)* **1941**, 556; **1942**, 257.

⁵⁶ For reviews on vinyl cations, see: (a) Stang, P. J.; Rappoport, Z.; Hanack, M.; Subramanian, L. R. *Vinyl Cations*, Academic Press: New York, 1979, pp 216-222. (b) Richey, H. G., Jr.; Richey, J. M. In *Carbonium Ions*; Olah, G. A.; Schleyer, P. v. R., Eds.; John Wiley and Sons: New York, 1970; Vol. 2, pp 947-949. (c) Hanack, M. *Acc. Chem. Res.* **1970**, *3*, 209.

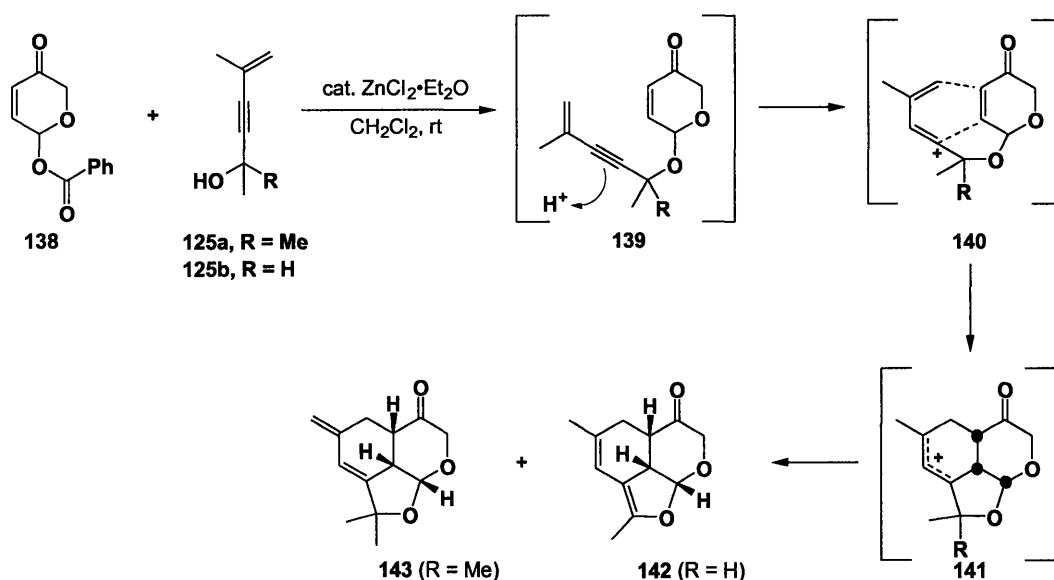
cation **133** then gives the aromatic product **134**. Although the most stable cation that can result from protonation of **130** is actually **135**, cation **131** is the one that leads to the formation of the observed product (**134**) following the Curtin-Hammett principle.



Cationic intermediates have been invoked in several other studies following Nazarov's report.⁵⁷ In particular, Hoffmann investigated several related enyne

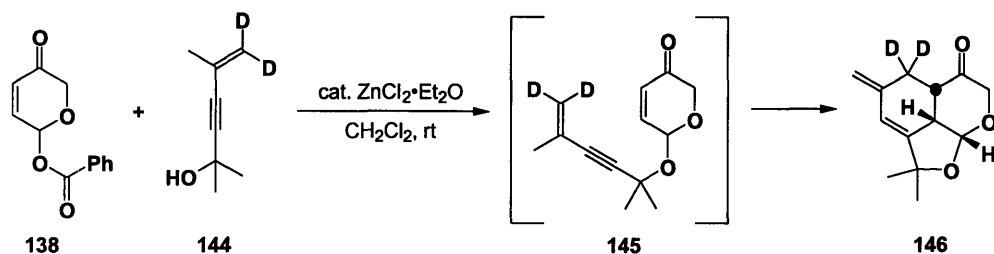
⁵⁷ (a) Whitlock, H. W.; Jr.; Wu, E.-M.; Whitlock, B. J. *J. Org. Chem.* **1969**, *34*, 1857. (b) Hakopian, L. A.; Gezalian, G. I.; Grigorian, S. G.; Matsoyan, S. G. *Arm. Khim. Zh.* **1974**, *27*, 764. (c) Hakopian, L. A.; Gezalian, G. I.; Matsoyan, S. G. *Arm. Khim. Zh.* **1974**, *27*, 768. (d) Hakopian, L. A.; Gezalian, G. I.; Matsoyan, S. G. *Arm. Khim. Zh.* **1975**, *28*, 72.

cycloadditions in detail, including protic and Lewis acid-promoted reactions.⁵⁸ When performing a transacetalization between enynols of type **125** and acetal **138** in the presence of Lewis acids, Hoffmann isolated tricyclic products **142** and **143**, presumably via acetal **139** which undergoes a [4+2] cycloaddition under the reaction conditions. Like Nazarov, Hoffmann proposed that contrathermodynamic protonation the enyne produces a vinyl cation, which upon cycloaddition and subsequent elimination in this case gives a mixture of conjugated dienes **142** and **143**.

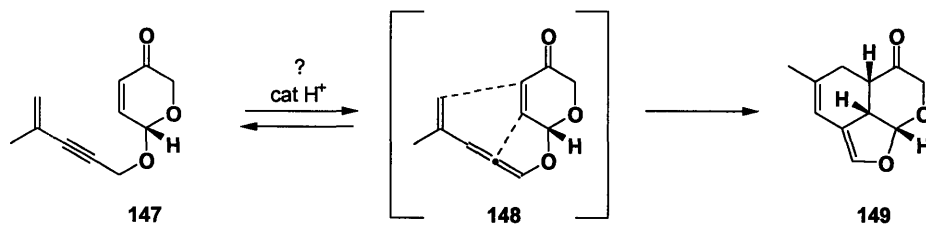


Hoffmann studied these reactions in more detail by performing isotopic labeling experiments with deuterated enyne **144** and reported neither loss nor scrambling of the deuterium labels in the tricyclic product. This demonstrated that protonation of the alkenyl portion of the enyne does not occur during this transformation, since the isotopic labels remained intact during the reaction. Hoffmann concluded that these cycloadditions proceed via a Diels–Alder reaction involving a dienyl cation that results from protonation of the alkynyl portion of the enyne.

⁵⁸ Hoffmann, H. M. R.; Krumwiede, D.; Mucha, B.; Oehlerking, H. H.; Prahst, G. W. *Tetrahedron*, **1993**, *49*, 8999.



An alternate Diels-Alder-type mechanism involving the initial isomerization of the enyne to a vinylallene was also considered by Hoffmann. Diels-Alder cycloadditions of vinylallenes are well-known and have been used to prepare bicyclic conjugated dienes similar to Hoffmann's product **142**.⁵⁹ Although this mechanism was considered as an alternative for the formation of **149**, two observations suggest this is not the general pathway involved in these reactions. First, the stereochemical integrity of substrates bearing a stereocenter at the propargylic position of the acetal was found to be conserved throughout the cycloaddition, whereas any conditions leading to the isomerization of the alkyne to an allene would have led to epimerization at this position. Second, substrates bearing geminal dimethyl substituents at the propargylic position, which are incapable of undergoing this isomerization, were found to effectively participate in the reaction.

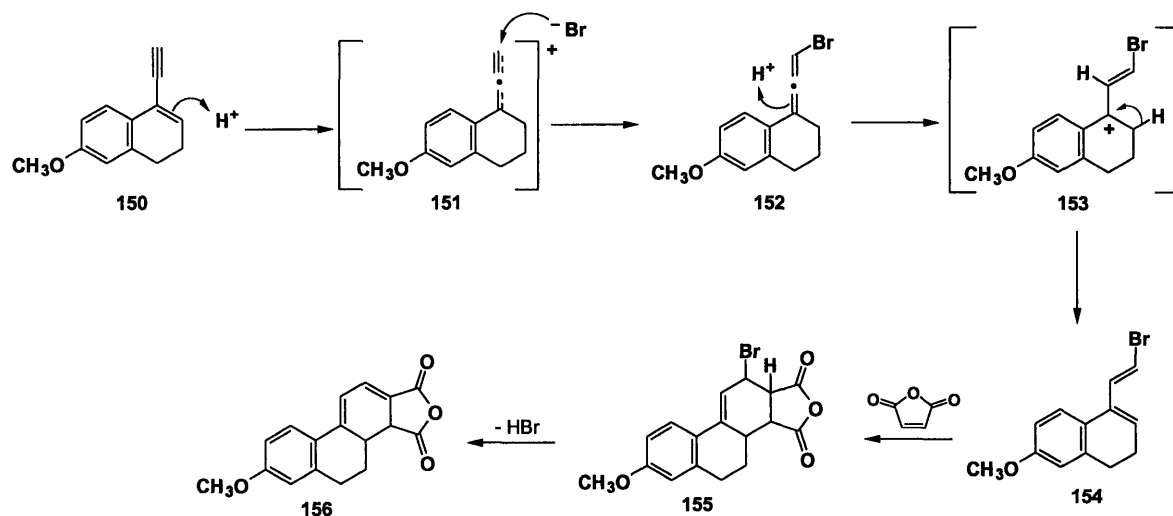


In 1996, Miller and Ionescu⁶⁰ proposed an alternate mechanism for enyne cycloadditions after unsuccessfully attempting to reproduce reactions originally reported by Dane in 1937.^{53a,b} Dane's cycloaddition was supposedly done under neutral conditions, but Miller suggested that traces of protic acid were most likely present in Dane's reaction mixture since he observed reaction to take place only when a catalytic

⁵⁹ For a review, see: Okamura, W. H.; Curtin, M. L. *Synlett* **1990**, 1.

⁶⁰ Miller, B.; Ionescu, D. *Tetrahedron Lett.* **1994**, 35, 6615. For Dane's work see references 52a and 52b.

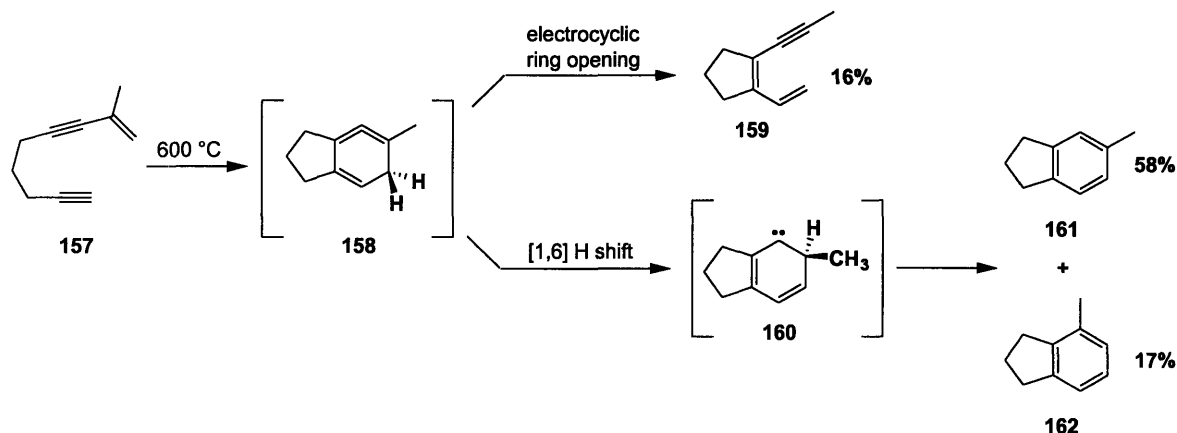
amount of HBr or HCl was added. Miller proposed that a catalytic amount of HX transforms Dane's substrate **150** into bromo diene **154** through an addition-elimination cascade. Bromo diene **154** can then undergo a Diels-Alder cycloaddition with maleic anhydride, followed by elimination of HBr to give the dihydroaromatic product **156**.



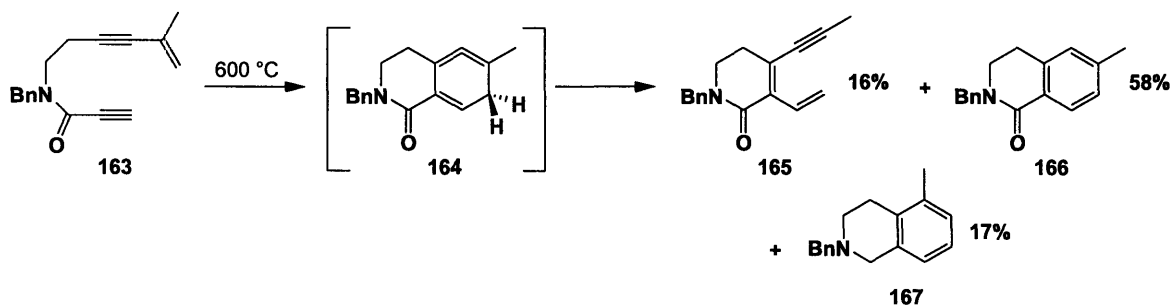
In contrast to the cationic mechanism proposed by Nazarov and Hoffmann, Miller and Ionescu suggested that protonation of **150** occurs at the *alkenyl* portion of the enyne. In substrate **150**, protonation of the double bond may be particularly favored due to the stabilizing effect of the *para*-methoxyphenyl group attached at the internal carbon of the alkene. Consequently, although this “halo diene” mechanism may be operating in the case of substrate **150**, it probably is not a general mechanism for enyne cycloadditions, since reactions of this type have been successfully carried out in the presence of acid scavengers,⁵⁰ⁱ as well as using amines as solvents or co-solvents.⁶¹ Results from our own experiments in which cycloadditions have been achieved in the presence of proton scavengers like 2,6-di-*tert*-butylpyridine and Me_2AlCl strongly suggest that protic acid is not a requirement for the reaction.

⁶¹ (a) Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **2002**, 43, 2717. (b) Rodríguez, D.; Castedo, L.; Domínguez, D.; Saá, C. *Org. Lett.* **2003**, 5, 3119. (c) Rodríguez, D.; Castedo, L.; Domínguez, D.; Saá, C. *Synthesis* **2004**, 761. (d) Rodríguez, D.; Martínez-Esperón, M. F.; Castedo, L.; Navarro-Vázquez, A.; Domínguez, D.; Saá, C. *J. Org. Chem.* **2004**, 69, 3842.

The question of whether [4+2] cycloadditions of conjugated enynes are concerted and proceed via the intermediacy of a six-membered, isoaromatic allene has been recently studied in our laboratory and by several other groups. In 1996, Johnson reported that flash vacuum pyrolysis (FVP) of enyne **157** results in three products, one of which (**159**) is most likely generated via the 6π electrocyclic ring opening of a cyclic allene intermediate (**158**).⁶²



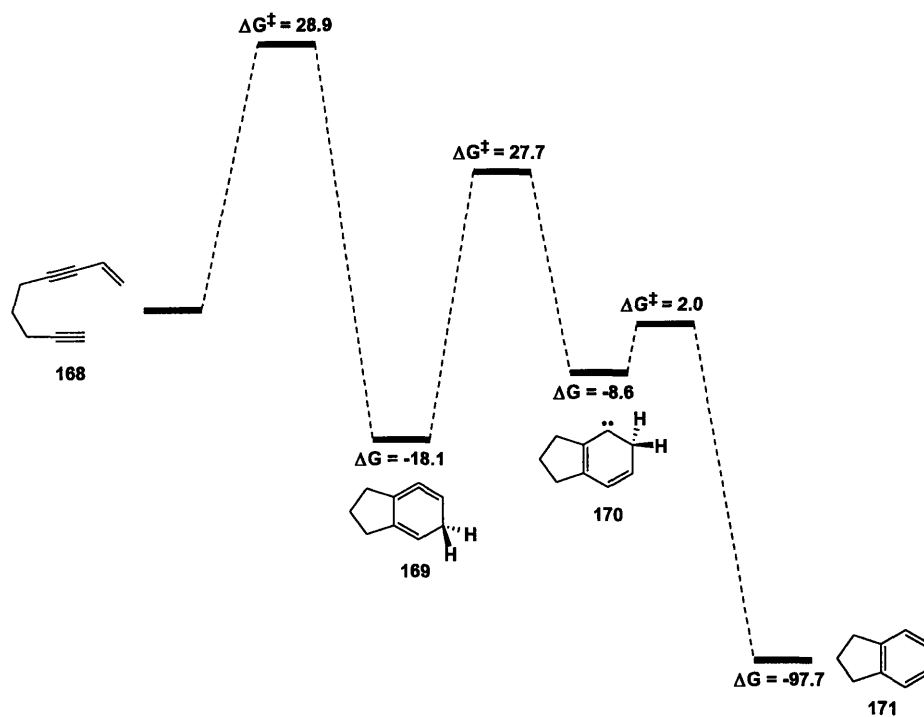
Brenda Palucki in our laboratory reported similar results in the FVP of enyne **163**. Thus, thermolysis of this enyne led to the formation of three compounds, **165**, **166**, and **167**, consistent with the intermediacy of allene **164**.^{6d}



A recent *ab initio* computational study by Ananikov suggests that a concerted mechanism involving a highly reactive cyclic allene intermediate is the lowest energy pathway for both inter- and intramolecular [4+2] enyne cycloadditions, with the energy

⁶² Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996**, *118*, 4218. Reported yields are from GC analysis.

values shown in the following scheme.⁶³ This study also supports the formation of the six-membered ring as being the rate-determining step for the overall process.



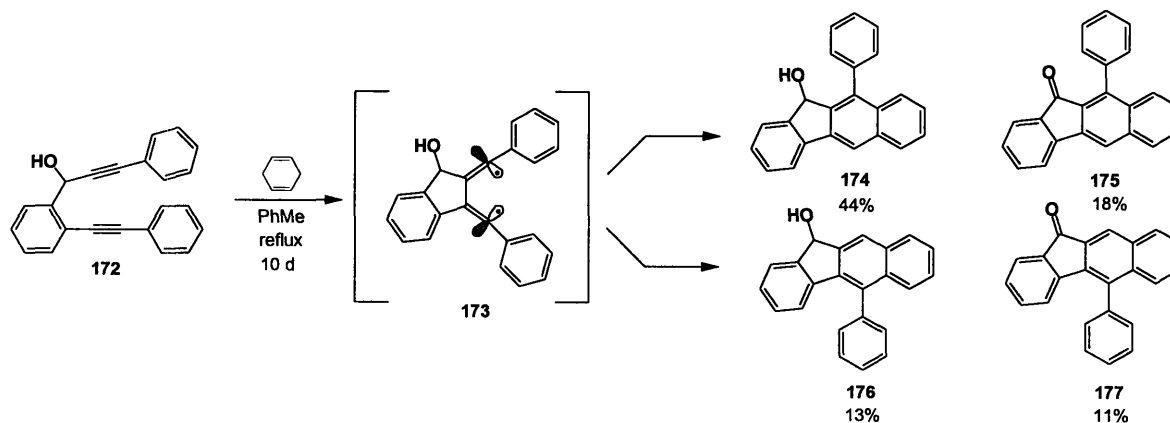
Various reports suggest that the mechanism of the cycloaddition of conjugated arenynes also involves a cyclic allene intermediate, although for these substrates the pathway leading to the cyclic allene may be stepwise.⁶⁴ In 1998, Schmittel reported the cycloaddition of arenynes **172** and suggested biradical **173** as an intermediate, proposing that radical stabilizing groups⁶⁵ promote a stepwise pathway in this reaction.⁶⁶

⁶³ Ananikov, V. P. *J. Phys. Org. Chem.* **2001**, *14*, 109. ΔG^\ddagger and ΔG values are in kcal/mol.

⁶⁴ (a) Bossenbroek, B.; Shechter, H. *J. Am. Chem. Soc.* **1967**, *89*, 7111. (b) Atienza, C.; Mateo, C.; de Frutos, O.; Echavarren, A. M. *Org. Lett.* **2001**, *3*, 153. See also work by Saá.⁶¹

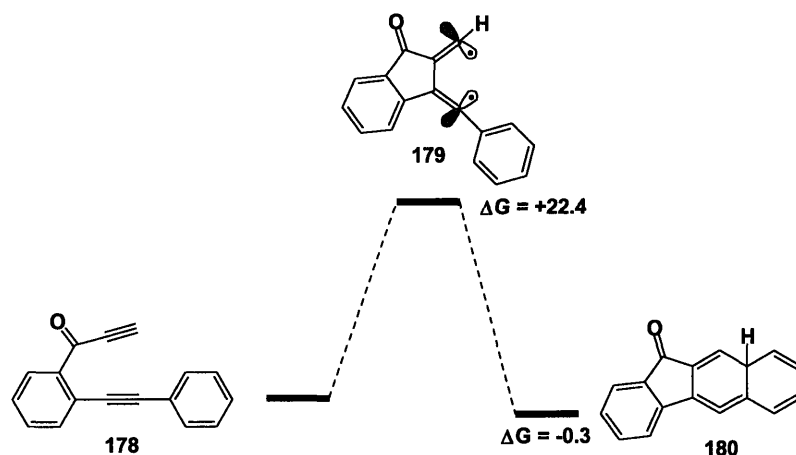
⁶⁵ For a review of radical stability and reactivity, see: Newcomb, M. In *Reactive Intermediate Chemistry*; Moss, R. A.; Platz, M. S.; Jones, M. Jr., Eds.; Wiley-VCH: Hoboken, NJ, 2004; Ch. 4, pp 121-164.

⁶⁶ Schmittel, M.; Strittmatter, M.; Schenk, W. A.; Hagel, M. Z. *Naturforsch.* **1998**, *53b*, 1015.

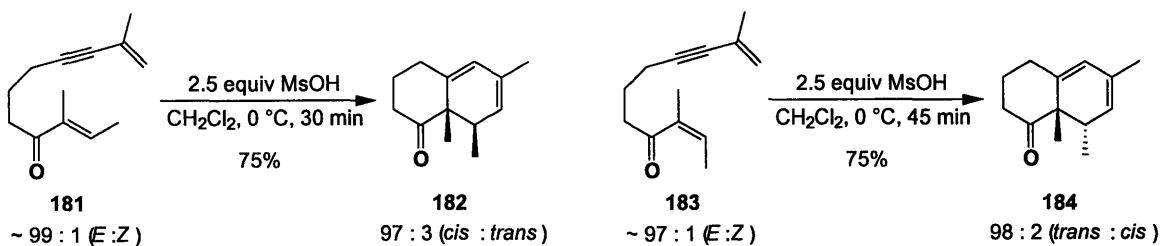


In a computational study by Saá, *ab initio* calculations comparing the concerted and stepwise pathways to the cyclic allene found energy minima only for the stepwise mechanism,⁶⁷ suggesting that the lowest energy pathway for the formation of allene **180** from substrate **178** involves biradical intermediate **179**. Although the biradical intermediates proposed for these stepwise pathways are likely very short-lived, their existence should have an impact on the energetics of the cycloaddition. As in Diels-Alder reactions, electron withdrawing groups (EWGs) attached to the 2π component tend to accelerate enyne and arenyne cycloadditions. Since most EWGs are also good radical stabilizing groups, it may be difficult to distinguish whether they affect the reaction via FMO energy perturbation or because of their ability to stabilize radicals. However, in Chapter 2 of Part II an example of a hetarenyne cycloaddition is presented in which an EDGs on the 2π component actually accelerates the reaction, which is suggestive of the existence of a biradical intermediate since EDGs tend to retard normal electron demand Diels-Alder reactions.

⁶⁷ Rodríguez, D.; Navarro, A.; Castedo, L.; Domínguez, D.; Saá, C. *Org. Lett.* **2000**, *2*, 1497.

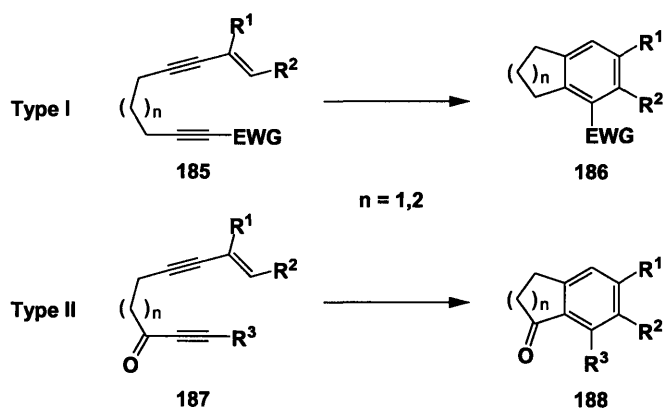


Prior research in the Danheiser group on enyne cycloadditions suggest that non-aromatic enyne cycloaddition substrates react via a concerted pathway. Experiments by Roberto Fernández de la Pradilla with substrates **181** and **183** containing *cis*- and *trans*-substituted alkenes as 2π components resulted in highly stereoselective reactions (unpublished results) consistent with a concerted suprafacial cycloaddition that translates the stereochemistry of the substrate to the product, although a very fast stepwise pathway cannot be discounted.



During the past fifteen years, many of the research efforts in the Danheiser group have focused on systematically studying the scope, applications, and mechanistic features of the intramolecular [4+2] cycloaddition of conjugated enynes. The substrates initially examined in our laboratory can be classified as either “Type I” or “Type II” depending on the position of attachment of the EWG within the tether connecting the 4π and 2π components. In “Type I” substrates, the EWG is attached to the terminus of the alkynyl

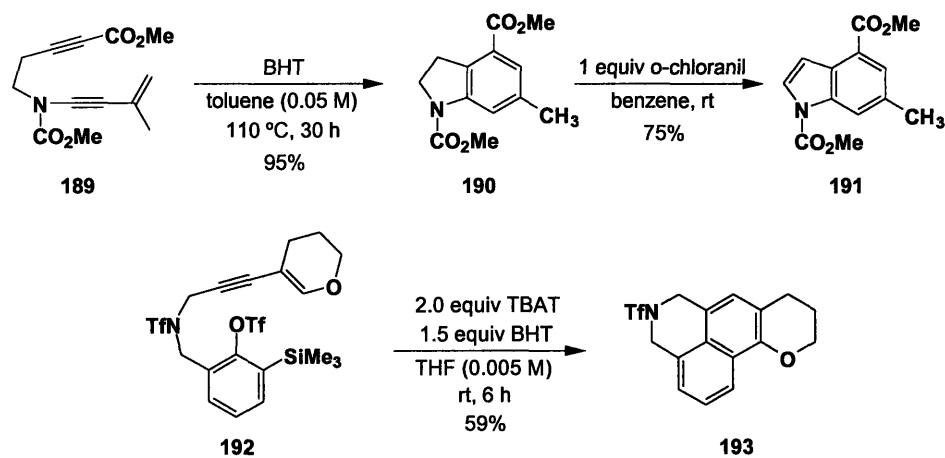
or alkenyl 2π component, whereas for “Type II” substrates the EWG is contained within the tether and is attached to the internal alkynyl carbon of the enynophile.



In general, the optimal conditions for effecting these cycloadditions involve heating a degassed, dilute (0.005-0.10 M) solution of the substrate in a solvent like toluene or benzene. The yield of the reaction benefits somewhat from the presence of phenolic additives like 2,6-di-*tert*-butyl-4-methylphenol (BHT), which can serve both as a proton source and radical scavenger, as well as the use of alcohols as co-solvents. As expected, enynophiles involving EWGs are especially reactive, requiring less time and lower temperature than alkynes lacking activating groups. When the activating group (e.g., carbonyl group) attached to the 2π component can interact with Lewis or protic acids, these additives can dramatically facilitate the cycloaddition, in many cases allowing the reaction to take place at or below room temperature. Lewis acid promotion is well

known in other cycloadditions like the Diels-Alder⁶⁸ and ene reactions, and our studies show a similar effect in enyne cycloadditions.⁶⁹

Initially the enyne cycloaddition studies in our laboratory focused on the synthesis of carbocyclic aromatic⁷⁰ and dihydroaromatic compounds,^{5a} but more recently this chemistry was expanded to include the synthesis of heterocycles,⁷¹ as well as the use of arynes as 2π components, as in the examples shown below.⁷²



⁶⁸ For reviews of the Diels-Alder reaction, including Lewis acid catalysis, see: (a) Konovalova, A. I.; Kiselev, V. D. *Russ. Chem. Bull., Int. Ed.* **2003**, *52*, 293. (b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (c) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 315-399. (d) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 513-550. (e) Ciganek, E. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1984, Vol. 32, pp 1-374. (f) Fringuelli, F. *The Diels-Alder Reaction*; John Wiley & Sons: New York, 2002; Ch. 3. (g) Roush, W. R. In *Cycloadditions*; Curran, D. P., Ed.; Jai: Greenwich, CT, 1990; Vol. 2, pp 91-146.

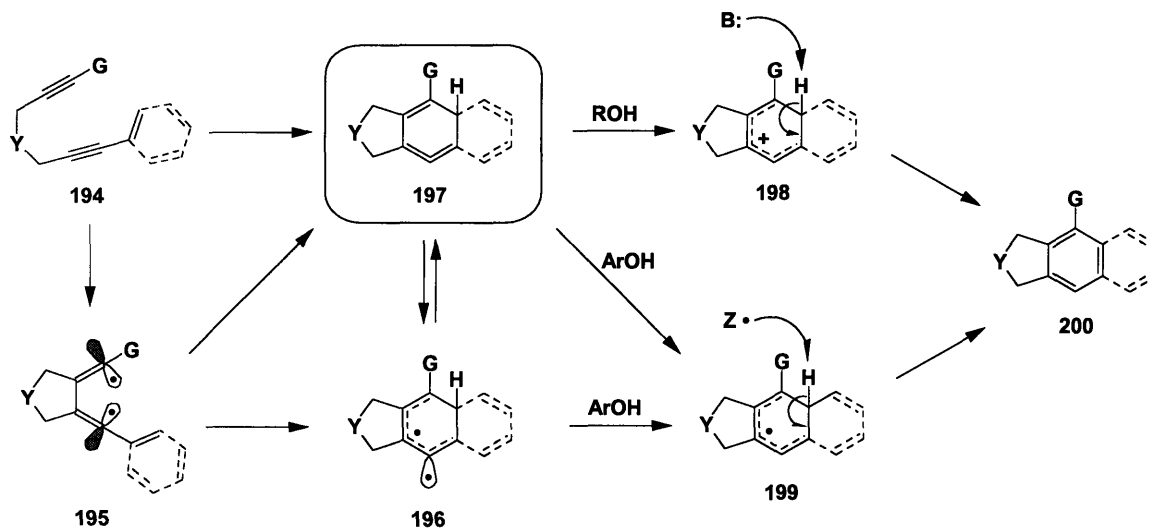
⁶⁹ For literature on Lewis acids in pericyclic reactions, see: (a) Maruoka, K.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 668. (b) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927. (c) *Lewis Acids and Selectivity in Organic Synthesis*; Santelli, M.; Rees, C., Eds.; CRC Press: Boca Raton, FL, 1996. (d) *Lewis Acid Reagents: A Practical Approach*; Yamamoto, H., Ed.; Oxford University Press: New York, 1999.

⁷⁰ For a review of methods for the synthesis of carbocyclic aromatic systems see: Williams, A. C. *Contemporary Org. Synthesis* **1996**, *3*, 535.

⁷¹ See references 5b, 5c, and 6a. Also see section 2.5 below.

⁷² See references 5d and 6b.

Based on the existing experimental and computational mechanistic studies described above, our current understanding of the mechanism of the enyne and arenyne cycloadditions in solution⁷³ is depicted below.



The generalized enyne cycloaddition substrate **194** can conceivably react to give cyclic allene intermediate **197** either in a stepwise or concerted fashion. As previously described, the stepwise pathway via biradical **195** is believed to be operating primarily in arenyne substrates where the substituents at the termini of the diyne structure have radical-stabilizing character (e.g., arenes, carbonyl groups, and heteroatoms like oxygen and nitrogen). Biradical **195** can collapse either to cyclic allene **197** directly, or to the alternate cyclic biradical **196**. Regardless of whether cyclic allene **197** forms via a concerted or stepwise pathway, this intermediate is the central player in this transformation, and its fate is determined by the reaction conditions. In the presence of reagents capable of donating protons and/or hydrogen atoms (e.g., phenolic compounds), the cyclic allene is believed to be transformed into either pentadienyl cation **198** or pentadienyl radical **199**. Intermediates **198** and **199**, although themselves

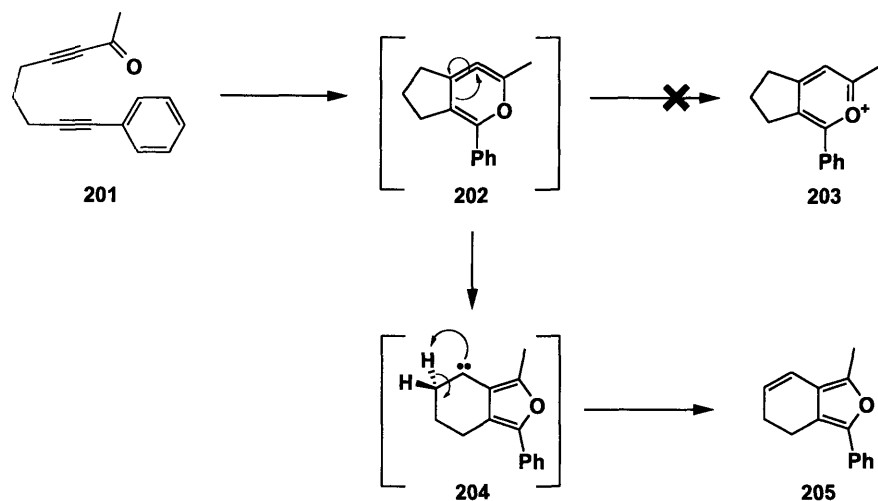
⁷³ In the gas phase the mechanism seems to involve a 1,6-sigmatropic rearrangement of cyclic allene **197** to a carbene, which then inserts into adjacent sp³ sigma bonds. This is exemplified by the experimental results for the formation of **161** and **162**, and is consistent with Ananikov's computational results.

very reactive, are believed to lead readily to the final aromatic product by simple elimination or loss of a hydrogen atom. Experiments conducted in our laboratory with phenolic compounds as additives have led to the conclusion that these compounds can facilitate the isomerization of the cyclic allene to the aromatic product via the pathways just described. These compounds seem to function either as a source of protons, hydrogen atoms, or both, depending on the nature of the substrate (*vide infra*).

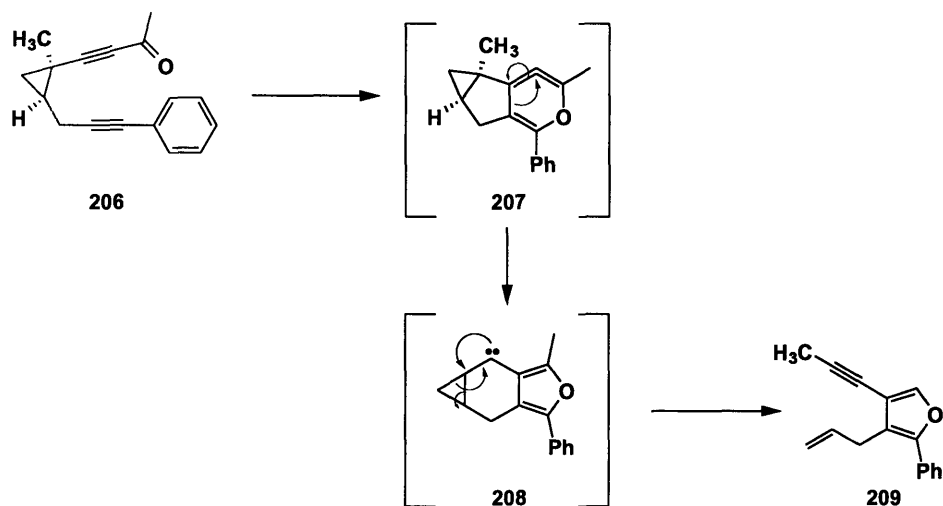
2.5. Cycloadditions Involving Heteroenynes

The reaction of heteroenynes has also been applied in our laboratory as a practical method for the synthesis of highly-substituted heteroaromatic compounds.^{5b} Acylsilanes and alkynyl aldehydes and ketones (ynones) can act as 4π components in intramolecular [4+2] cycloadditions with alkynes to furnish dihydroisobenzofurans by an unusual rearrangement discovered in the Danheiser group. In an analogous fashion to the reactions described in the previous section, the initial cycloaddition is believed to generate a heterocyclic allene intermediate of type **202**, which instead of being protonated to form the pyrilium cation **203** undergoes a 1,2-carbon shift to generate a furylcarbene, **204**. The carbene then undergoes a C-H insertion to give the dihydroisobenzofuran **205**.⁷⁴

⁷⁴ Recent ab-initio calculations predict an alternative [3+2] cycloaddition that forms the furylcarbene directly. See: Ananikov, V. P. *J. Phys. Org. Chem.* **2003**, *16*, 253.



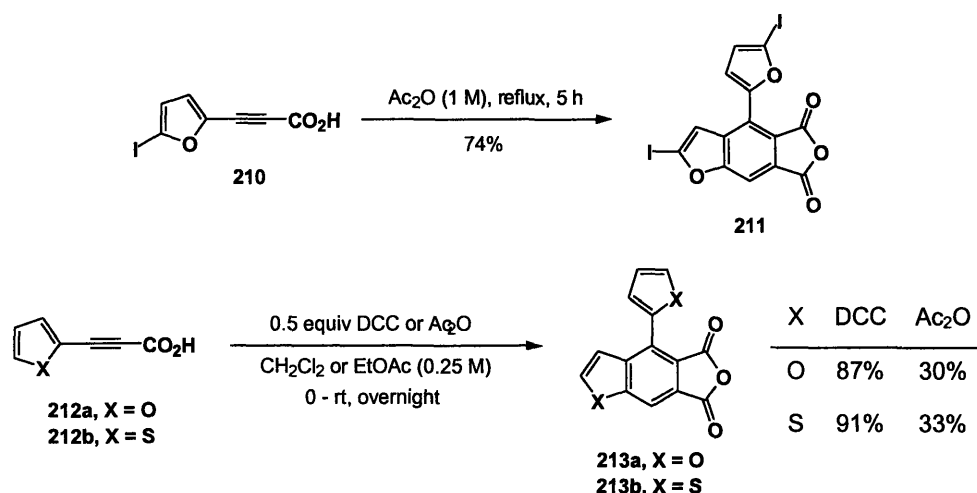
Like the enyne cycloaddition, the [4+2] cycloaddition of ynones can be performed with a variety of substituents and tether compositions.⁷⁵ The intermediacy of carbene **204** was established by examining the reaction of substrate **206**, which fragments to yield furan **209**, as expected if the proposed mechanism is operating.



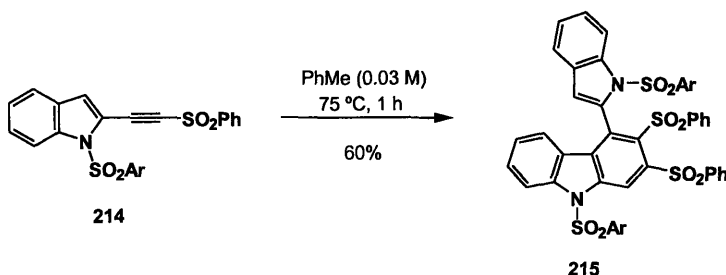
⁷⁵ For a full account of the scope, limitations, and mechanism of this reaction, see: (a) Wills, M. S. B. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1998. (b) Diffendal, J. M. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 2002. Also see reference 5b.

2.6. Cycloadditions Involving Hetarenynes

Only scattered examples exist of cycloadditions involving “hetarenynes” (i.e., heteroaromatic rings substituted with alkynyl groups). In 1965, the first heterocyclic variant of the Michael-Bucher reaction appeared with the report by Vereshchagin that halo-substituted furylpropionic acids give benzofurans upon heating in acetic anhydride,⁷⁶ a reaction that was explored further by Cadby in the 1970s.⁷⁷



More recently, Passarella has reported the serendipitous formation of carbazoles resulting from dimerization of certain alkynyl indoles via an intermolecular [4+2] cycloaddition. Only substrates bearing EWGs on the nitrogen and the alkyne were found to participate in this transformation, as in the example shown below.⁷⁸ This is the first and only report, to our knowledge, of a successful intermolecular arenyne cycloaddition.



⁷⁶ Vereshchagin, L. I.; Korshunov, S. P.; Aleksandrov, S. L.; Bol'shedvorshaya, R. L. *J. Org. Chem. USSR (Engl. Transl.)* **1965**, *1*, 967; *Z. Org. Khim.* **1965**, *1*, 960.

⁷⁷ Cadby, P. A.; Hearn, M. T. W.; Ward, A. D. *Aust. J. Chem.* **1973**, *26*, 557.

⁷⁸ Passarella, D.; Giardini, A.; Martinelli, M.; Silvani, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 127.

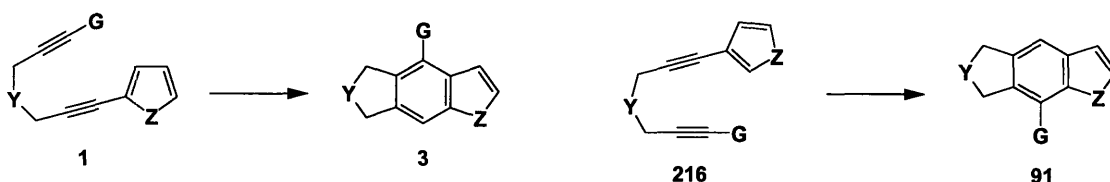
None of these studies with hetarenynes focused on studying the scope and applications of this transformation. With the vision that this reaction could be used as an efficient method for the synthesis of benzo-fused, five-membered heteroaromatic compounds, we decided to begin a systematic investigation of the applicability of the hetarenyne cycloaddition chemistry, as described in detail in the next section.

Part II:
Hetarynyne Cycloadditions
Results and Discussion

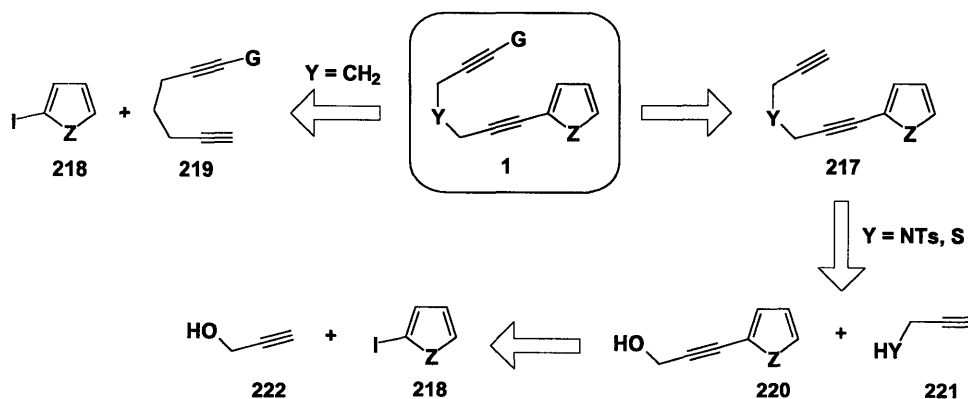
Chapter 1. Assembly of Hetarenyne Cycloaddition Substrates

The primary objectives of our studies of the hetarenyne cycloaddition reaction were to study the feasibility of the reaction as a synthetic tool as well as to develop an efficient method for the synthesis of benzo-fused, five-membered heterocyclic compounds. Our aim was to carry out a systematic investigation of the scope and limitations of the cycloaddition focusing on how the rate and efficiency of the reaction is affected by:

- (1) Different activating groups (G) attached to the 2π component
- (2) The presence of heteroatoms (Y) within the tether
- (3) The type of hetarene (Z = NR, O, S)
- (4) The position of attachment of the tether to the hetarenyne ring (i.e., C-2 as in **1** or C-3 as in **216**)



Our general approach to the assembly of the cycloaddition substrates employed in the investigation is outlined below:



Generic hetarenyne cycloaddition substrate **1** can originate from elaboration of terminal alkynes of type **217** via metalation and addition to an appropriate electrophilic

reagent. When the tether of diyne **217** contains a nucleophilic heteroatom (e.g. Y = NTs or S), then Mitsunobu coupling⁷⁹ of a hetaryl propargylic alcohol **220** with a propargylic sulfonamide⁸⁰ or thiol **221** can provide the diyne. Hetaryl propargylic alcohols of type **220** can be obtained from the Sonogashira coupling⁸¹ of hetaryl halides⁸² **218** and propargyl alcohol. In the case of cycloaddition substrates with all-carbon tethers, Sonogashira coupling of a hetaryl halide **218** with commercially available 1,6-heptadiyne or a mono-substituted derivative provides the key intermediate. Thus, in most cases the requisite cycloaddition substrates can be prepared in 2-3 steps from a readily available halopyrrole, -furan, or -thiophene.

The synthesis of the 2-tethered pyrrole substrates begins with 2-iodo-*N*-(*t*-butoxycarbonyl)pyrrole (**226**), which is not commercially available. The only published synthesis of this compound was reported by Cava in 1987.^{83a} This method involves the initial preparation of 2-bromo-*N*-(*t*-butoxycarbonyl)pyrrole (**225**)⁸³ from pyrrole, followed by metalation with *n*-BuLi, and addition of elemental iodine, as shown below. This method provides **225** in very good yield (87% originally reported by Cava) and we have obtained the iodide in up to 88% yield in our laboratory using this method.

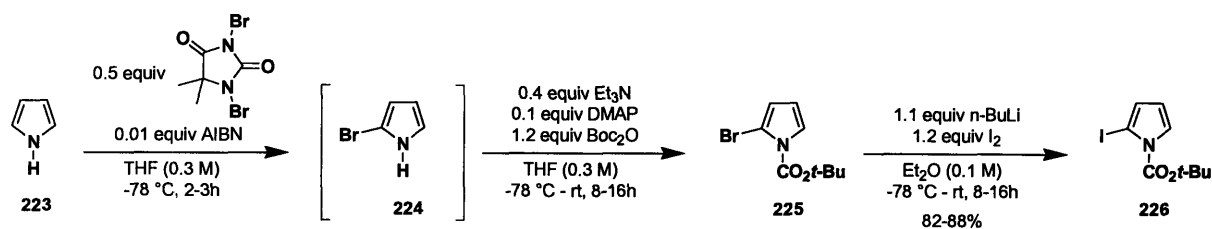
⁷⁹ For reviews of the Mitsunobu reaction, see: (a) D. L. Hughes, *Org. Prep. Proced. Int.* **1996**, *28*, 127. (b) D. L. Hughes, *Org. React.* **1992**, *42*, 335. (c) Dembinski, R. *Eur. J. Org. Chem.* **2004**, *13*, 2763.

⁸⁰ For Mitsunobu reactions involving sulfonamides, see (a) Tsunoda, T.; Yamamoto, H.; Goda, K.; Ito, S. *Tetrahedron Lett.* **1996**, *37*, 2457 and (b) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, Jr., G. D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.

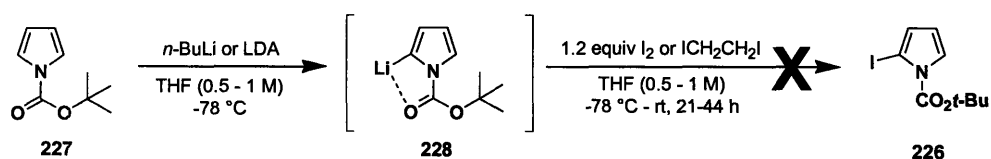
⁸¹ For a review of the Sonogashira reaction, see: (a) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998, pp 203-229. (c) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; pp 493-529.

⁸² For reviews of cross-coupling reactions of hetarenes, see: (a) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. (b) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*; Pergamon: Oxford, UK, 2000.

⁸³ (a) Chen, W.; Cava, M. *Tetrahedron Lett.* **1987**, *28*, 6025. (b) Chen, W.; Stephenson, E. K.; Cava, M.; Jackson, Y. A. in *Organic Syntheses*; Wiley & Sons: New York, 1998, Collect. Vol. No. 9, p 121



We also investigated the possibility of generating the desired iodide **226** by direct lithiation and iodination of pyrrole derivatives or by electrophilic iodination. Initial attempts were based on the directed metalation of commercially available *N*-(*t*-butoxycarbonyl)pyrrole (**227**) at the C-2 position of the ring using *n*-BuLi or LDA followed by reaction with elemental iodine or its equivalent. Although 2-substituted *N*-(*t*-butoxycarbonyl)pyrroles have been successfully synthesized by this method using a variety of electrophiles, including chlorotrimethylsilane, acetic anhydride, and acetaldehyde,⁸⁴ the use of iodine as an electrophile has not been reported. When attempting to trap the 2-lithiated pyrrole **228** with either iodine or 1,2-diiodoethane, only unreacted starting material was recovered and none of the desired iodide **226** was obtained.

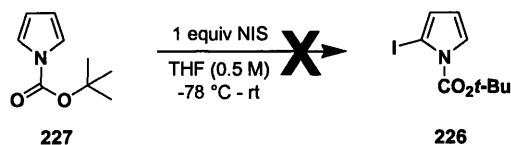


An alternate method for the synthesis of **226** was then examined based on electrophilic aromatic substitution (EAS). In 1949, Doak reported the iodination of various pyrrole derivatives bearing electron withdrawing substituents on the ring.⁸⁵ Treatment of these substituted pyrroles with elemental iodine in aqueous methanol solution in the presence of sodium bicarbonate furnished the corresponding iodopyrroles in good yield. Thirty years later, Gilow reported the efficient preparation of 2-

⁸⁴ Hasan, I.; Marinelli, E. R.; Lin, L. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.

⁸⁵ Doak, K. W.; Corwin, A. H. *J. Am. Chem. Soc.* **1949**, *71*, 159.

bromopyrrole and various *N*-alkyl derivatives by treating the corresponding pyrroles with NBS in THF.⁸⁶ Based on Doak's and Gillow's reports, the direct iodination of *N*-(*t*-butoxycarbonyl)pyrrole (**227**) was attempted with NIS, but again only unreacted starting material was recovered.

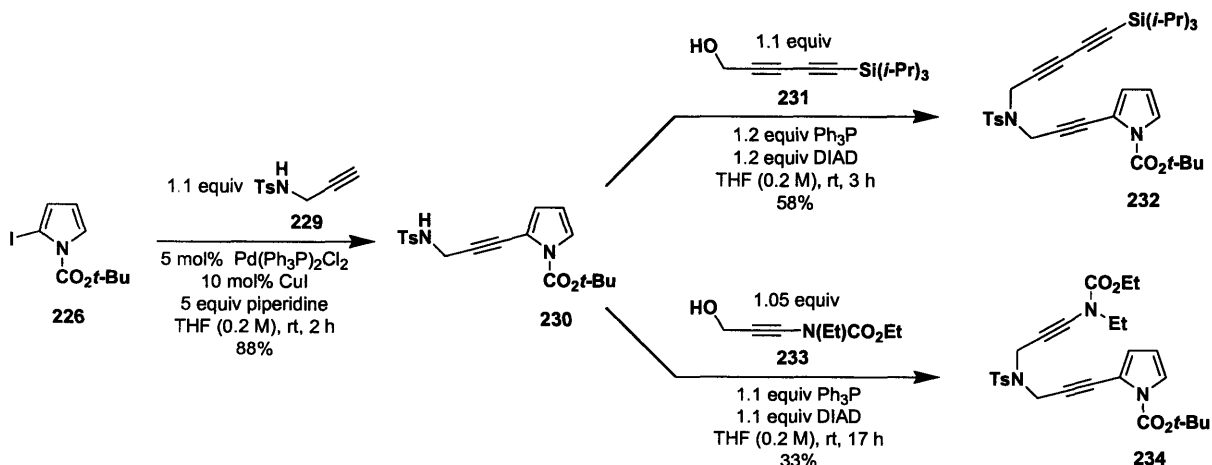


As indicated by Cava in his procedure, the synthesis of 2-bromo-*N*-(*t*-butoxycarbonyl)pyrrole (**225**) by the Cava procedure was found to be somewhat delicate, as the rate of addition of the brominating agent (1,3-dibromo-5,5-dimethylhydantoin) greatly affected the outcome of the reaction. Rapid addition resulted in the production of a mixture of monobromo, dibromo, and dehalogenated pyrroles, therefore, slow addition of the hydantoin as prescribed in the *Organic Syntheses* procedure^{83b} is critical to ensure clean production of the desired monobrominated product. The choice of solvent for the halogen exchange step is also crucial. Using THF resulted in mixtures ranging from 60:40-87:13 of halogenated(**226**):dehalogenated(**227**) compounds, regardless of whether the THF was dried by pressure filtration through activated alumina or distilled from sodium benzophenone ketyl. An explanation of this problem is still lacking, and no complication of this type is mentioned in the Cava procedure. Fortunately, we found that when using diethyl ether the reaction proceeds much more cleanly, in most cases furnishing the desired product **226** with only traces of the dehalogenated product, and at worst only 6% of **227**. Purification of both halogenated *N*-*t*-butoxycarbonyl (*N*-Boc) pyrroles **225** and **226** was possible with Et₃N-treated silica gel using hexanes as the eluent. The brominated pyrrole **225** could be stored as a solution in hexanes in the presence of Et₃N or piperidine for a few months;

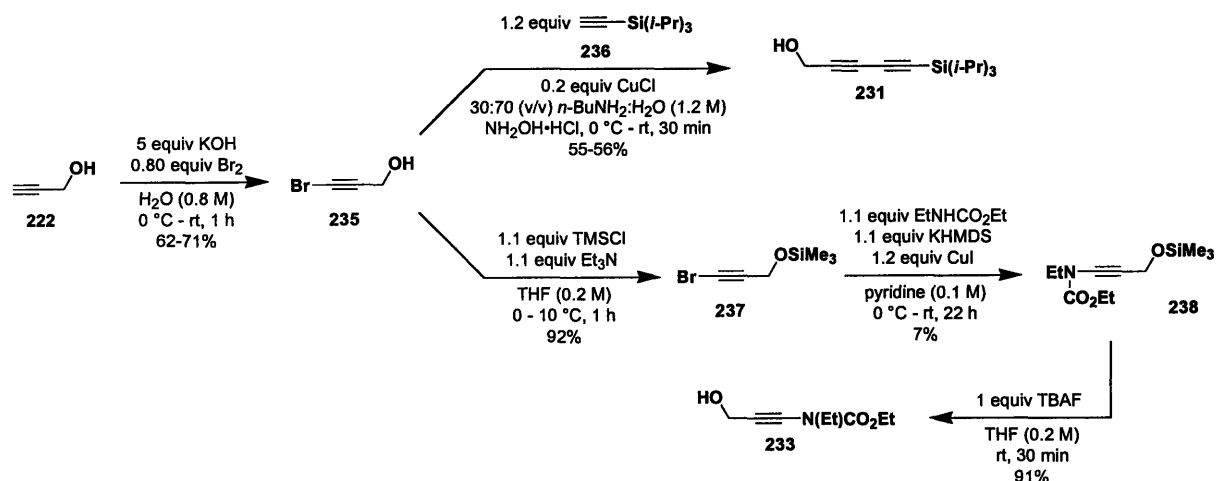
⁸⁶ Gilow, H. M.; Burton, D. E. *J. Org. Chem.* **1981**, *46*, 2221.

however, the iodopyrrole **226** was much less stable to long-term storage and only lasted for a few days under the same conditions. Therefore, usually the 2-bromopyrrole **225** was made in large batches and converted to the iodide **226** immediately before use in subsequent reactions.

With the 2-iodo-*N*-(*t*-butoxycarbonyl)pyrrole (**226**) in hand, the relatively straightforward assembly of the heteroene cycloaddition substrates was undertaken. Alkynylation of **226** with propargylic sulfonamide **229** (see below for preparation) was performed via the Sonogashira coupling using conditions previously employed in our group with other aryl iodides. This chemistry provided alkynyl pyrrole **230** in very good yield, so no optimization of the alkynylation conditions was deemed necessary. The highly convergent preparation of diyne **232** and ynamide **234** via Mitsunobu coupling was then possible using alcohols **231** and **233**, respectively (the preparation of these alcohols is discussed below). The isolation of pure **232** was a bit tricky, since the substrate is so reactive that cycloaddition was already evident during its purification. In addition to the 58% of pure diyne **232** isolated, 13% of a mixture of **232** and its cycloadduct (**310**) was also obtained from the chromatographic purification of **232**. The relatively low yield obtained in the preparation of **234** represents a single small scale run which was not optimized and most likely reflects the relative instability of alcohol **233**.



Propargylic sulfonamide **229** was prepared via a modification of previously reported procedures.⁸⁷ Our modified procedure utilized the solid hydrochloride salt of propargylamine (rather than the liquid free amine) due to ease of handling. Reaction of the solid ammonium salt with *p*-toluenesulfonyl chloride in the presence of 5 equivs of pyridine furnished the sulfonamide **229** in excellent yield (91-98%), considerably higher than previously reported. Diynol **231** was prepared as outlined below using the route previously published,⁸⁸ and the hydroxymethyl ynamide **233** was prepared using the ynamide chemistry developed in our group^{5c} beginning with propargyl alcohol as shown below.

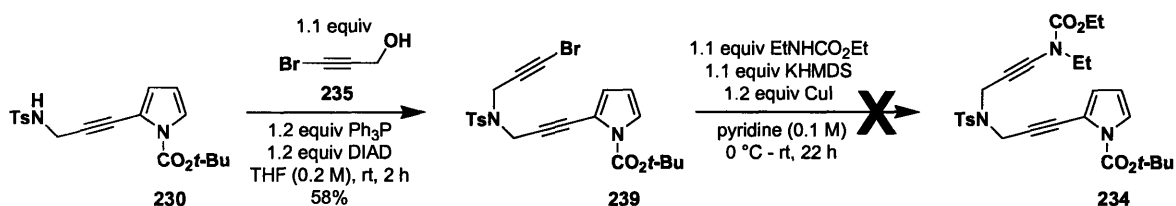


The low yield obtained in the preparation of the ynamide **238** is most likely due to the loss of the trimethylsilyl protecting group during chromatographic purification of the product. Since enough material was obtained in the single run carried out to provide an adequate supply of **233**, optimization of the synthesis of the ynamide **238** was not necessary. The route described above was not the first one attempted for the preparation of ynamide cycloaddition substrate **234**. Shown below is the initial route that was examined. This approach involved the attempted *N*-alkynylation of

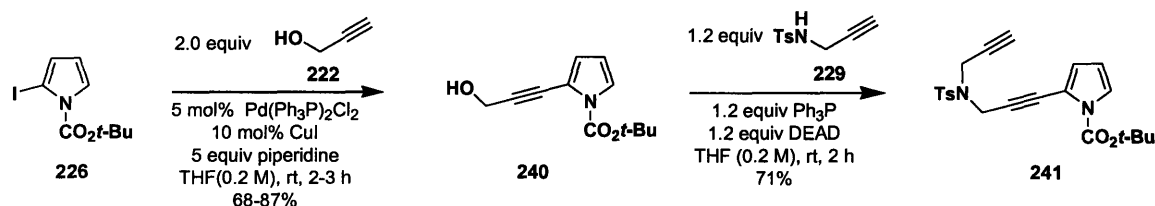
⁸⁷ (a) Oppolzer, W.; Ruiz-Montes, J. *Helv. Chim. Acta* **1993**, *76*, 1266. (b) Masquelin, T; Obrecht, D. *Synthesis* **1995**, *3*, 276.

⁸⁸ Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6844.

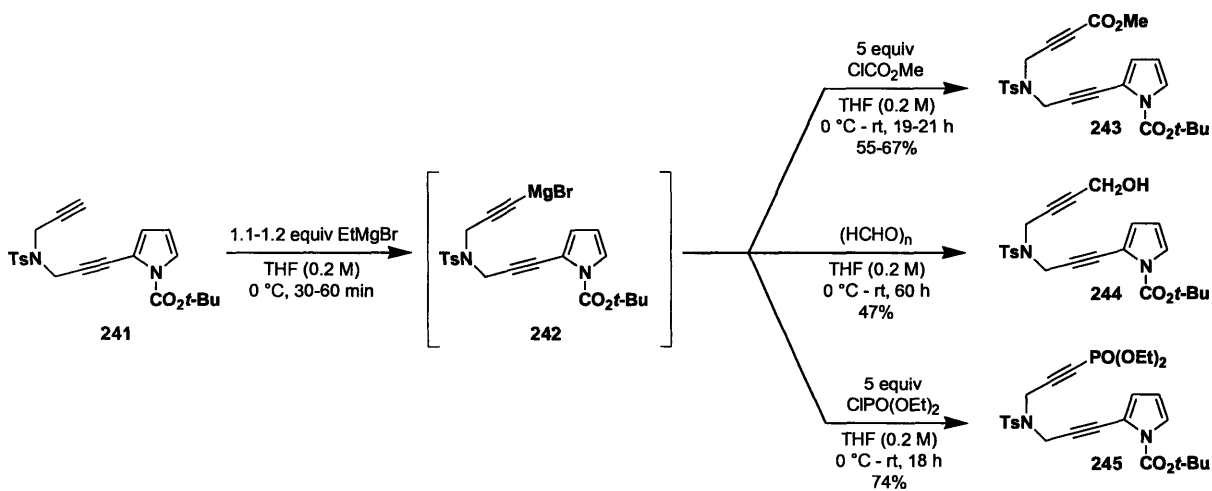
EtNHCO₂Et with alkynyl bromide **239**, but unfortunately subjecting **239** to the typical reaction conditions for this transformation led to decomposition of the starting material and none of the desired ynamide **234** was obtained.



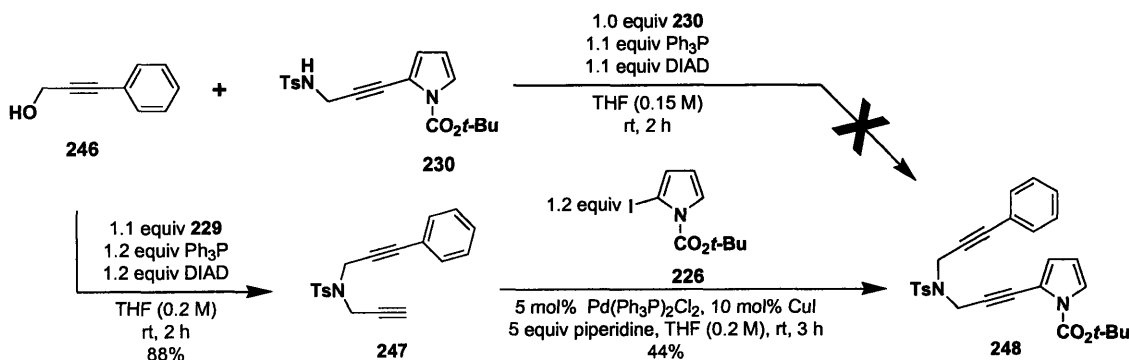
Cycloaddition substrates **243**, **244**, and **245** were all prepared via a common diyne intermediate, **241**. In similar fashion to that described above, alkylation of 2-iodopyrrole **226** with propargyl alcohol furnished propargylic alcohol **240**, which then combined with sulfonamide **229** in a Mitsunobu reaction to furnish terminal alkyne **241**.



The alkyne **241** was then metalated with EtMgBr and treated with methyl chloroformate, paraformaldehyde, and diethyl chlorophosphonate under the indicated conditions to furnish ester **243**, alcohol **244**, and phosphonate **245**, respectively. Using a large excess (i.e., 5 equiv) of the electrophile was found to give the best yields.



The synthesis of a pyrrole substrate with a phenyl group attached to the 2π component was also carried out as outlined in the scheme below. Our initial approach was based on the same convergent strategy used for the synthesis of diyne **232**, ynamide **234**, and alkynyl bromide **239**. Thus, coupling of sulfonamide **230** under Mitsunobu conditions with the propargylic alcohol **246**⁸⁹ produced the desired diyne **248**; however, this route was abandoned because of difficulties in separating the product from unreacted **246** and **230** using chromatography. An alternate approach involving Sonogashira coupling of 2-iodopyrrole **226** and diyne **247**⁹⁰ was ultimately used successfully to prepare **248**. The low yield in this Sonogashira reaction (carried out only once) was attributed to the use of 2-iodopyrrole **226** that had partially decomposed during storage.



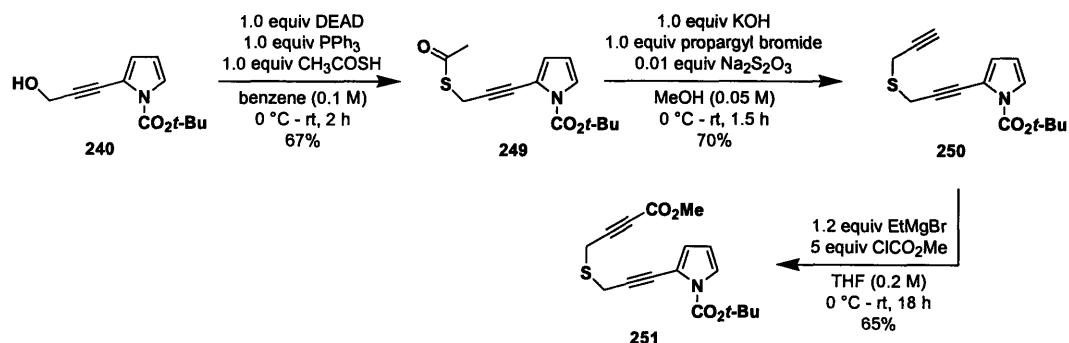
The synthesis of an alkynyl pyrrole cycloaddition substrate with a sulfur atom in the tether is outlined below. The preparation of terminal alkyne **250** began with propargylic alcohol **240** (*vide supra*) and involved introduction of the sulfur via a Mitsunobu reaction with thioacetic acid as previously reported with other propargylic alcohols.⁹¹ The thioester **249** was then hydrolyzed with base, and alkylation of the resulting thiolate salt with propargyl bromide gave terminal alkyne **250**. Metalation of

⁸⁹ Prepared via Sonogashira coupling of commercially available iodobenzene and propargyl alcohol (90%). This compound was previously reported by Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691.

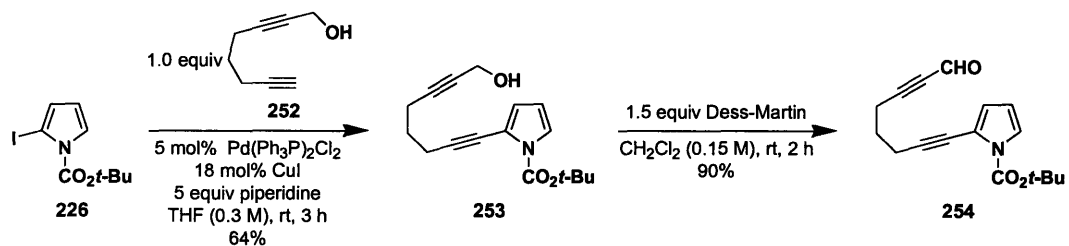
⁹⁰ Prepared via Mitsunobu coupling of propargylic alcohol **246** and sulfonamide **229** (88%).

⁹¹ Cao, X.; Yang, Y.; Wang, X. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2485.

250 with EtMgBr followed by treatment with methyl chloroformate furnished alkynyl ester **251**.



The preparation of the all-carbon-tethered pyrrole cycloaddition substrates required a somewhat different approach. The synthesis of alkynyl aldehyde **254** began with the Sonogashira coupling of 2-iodopyrrole **226** and alkyne **252**.⁹² Dess-Martin oxidation⁹³ of the resulting propargylic alcohol **253** gave alkynyl aldehyde **254**.



The synthesis of the all-carbon tethered alkynyl ester **258** was a bit more difficult. A route to this compound was initially developed serendipitously when attempting to synthesize the analogous *N*-Boc pyrrole from aldehyde **255**⁹⁴ via the recently reported one-pot procedure for transforming aldehydes into alkynes using dimethyl-1-diazo-2-oxopropylphosphonate (**256**).⁹⁵ Under these reaction conditions, the reaction medium

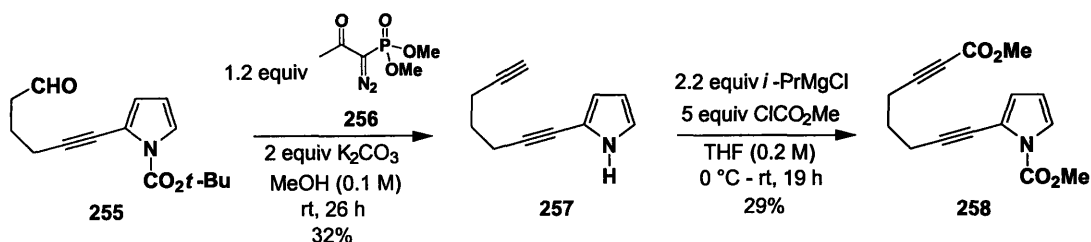
⁹² Prepared via single metalation of 1,6-heptadiyne with EtMgBr, followed by reaction with paraformaldehyde (47%). This compound was similarly prepared by: López, S.; Fernández-Trillo, F.; Castedo, L.; Saá, C. *Org. Lett.* **2003**, *5*, 3725.

⁹³ For reviews of the Dess-Martin oxidation and related chemistry, see (a) Zhdankin, V. V. *Curr. Org. Synth.* **2005**, *2*, 121. (b) Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111 and references cited therein.

⁹⁴ Prepared via Sonogashira coupling of 2-iodopyrrole **226** and commercially available 5-hexyn-1-ol (78%), followed by Dess-Martin oxidation (64%).

⁹⁵ (a) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59. (b) Meffre, P.; Hermann, S.; Durand, P.; Reginato, G.; Riu, A. *Tetrahedron* **2002**, *58*, 5159.

is sufficiently basic⁹⁶ to lead to the loss of the *N*-Boc protecting group, thus producing deprotected pyrrole **257** rather than the desired *N*-Boc derivative. Double metalation of **257** with excess *i*-PrMgCl followed by reaction with excess methyl chloroformate provided the *N*-carbomethoxy alkynyl ester **258**. These reactions were not optimized and the low yields are attributed to decomposition of pyrrole **257** during storage before its elaboration to **258**.

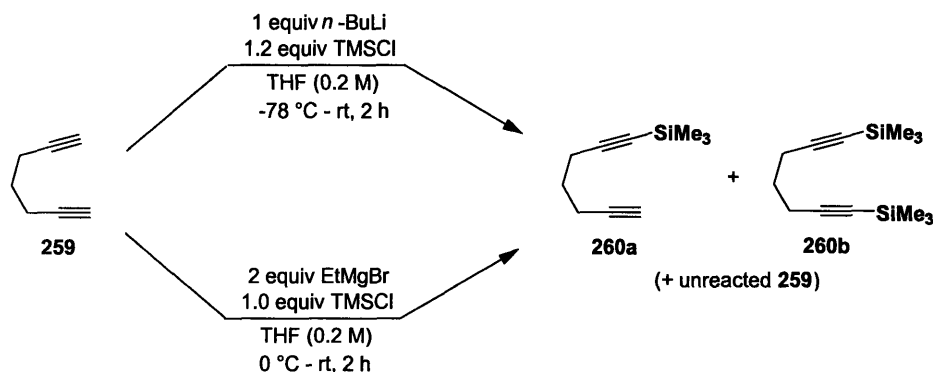


In an attempt to improve the yield and the efficiency of the preparation of cycloaddition substrate **258**, an alternate route was later pursued involving the Sonogashira coupling of 2-iodopyrrole **226** with monosubstituted 1,6-heptadiynes bearing an easily removable group that could later be replaced with a carboalkoxy group. The first approach of this type involved the direct monosilylation of 1,6-heptadiyne via metalation with *n*-BuLi followed by reaction with chlorotrimethylsilane. This transformation was reported previously in 65% yield using EtMgBr, although no experimental details were provided.⁹⁷ In our hands, this reaction produced a mixture of unreacted starting material **259**, the desired monosilyl diyne **260a**, and some bis-silylated material **260b**. Unfortunately, the volatility of the monosilyl product **260a** and starting material **259** made their separation very difficult, and these compounds also were inseparable by chromatography. A second attempt was made using a procedure

⁹⁶ For literature on methods to remove *N*-Boc protecting groups under basic conditions, see: (a) Hasan, I.; Marinelli, E. R.; Lin, L. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157. (b) Kline, T. J. *Heterocyclic Chem.* **1985**, *22*, 505. (c) Tom, N. M.; Simon, W. M.; Frost, H. N.; Ewing, M. *Tetrahedron Lett.* **2004**, *45*, 905.

⁹⁷ See: Bao, J.; Wulff, W. D.; Dragisich, J. V.; Wenglowksy, S.; Ball, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7616.

previously used in the group involving double metalation of the diyne with EtMgBr, followed by addition of one equivalent of chlorotrimethylsilane.⁹⁸ This method, however, also yielded a mixture of compounds.

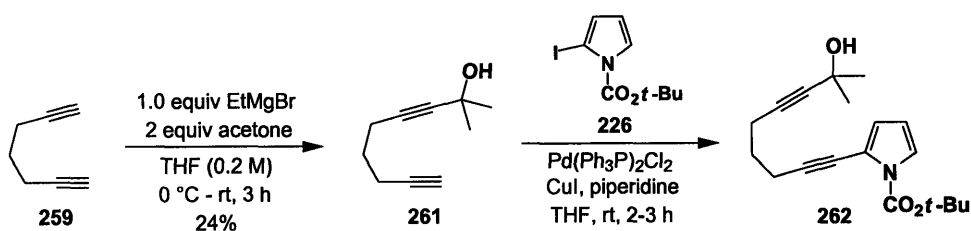


An alternative strategy was next examined in which 1,6-heptadiyne would be monoprotected with a *polar* removable group. This strategy was expected to lead to a decrease in both the R_f and volatility of the monosubstituted product, thereby allowing for its separation from any unreacted starting material and doubly protected diyne. Acetone was chosen as the reagent for monoprotection of **259**, since the cleavage of tertiary (dimethyl)alkynyl alcohols can be accomplished by heating with base.⁹⁹ This method seemed attractive because during this deprotection step it was deemed possible to also remove the *N*-Boc group protecting the pyrrole, thus furnishing **257** in one step. The exchange of the *N*-Boc protecting group for the *N*-carbomethoxy moiety was necessary for our studies of cycloadditions involving pyrrole substrates using Lewis acidic conditions, since reaction of *N*-Boc-protected pyrrole substrates with Lewis acids can lead to decomposition (*vide infra*).

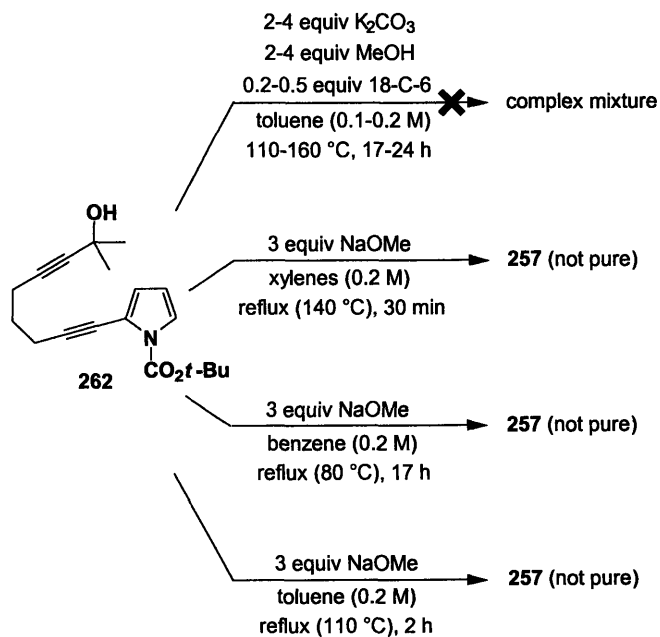
⁹⁸ Bartow-Wills, M. S., Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1998, p 204.

⁹⁹ For examples of typical conditions see (a) Boyall, D.; López, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233. (b) Lee, M.; Kim, J.; Peleshanko, S.; Larson, K.; Yoo, Y.; Vaknin, D.; Markutsya, S.; Tsukruk, V. V. *J. Am. Chem. Soc.* **2002**, *124*, 9121. (c) Viala, C.; Secchi, A.; Gourdon, A. *Eur. J. Org. Chem.* **2002**, *24*, 4185.

In the event, monoprotection of 1,6-heptadiyne (**259**) with acetone was successfully accomplished, albeit in low yield due to the concomitant formation of the doubly-substituted product, which seems inevitable regardless of how much care is taken to avoid its formation. With a clean sample of the monoprotected 1,6-heptadiyne in hand, Sonogashira coupling with iodopyrrole **226** was the next step. At the time, only an impure sample of 2-iodopyrrole **226** contaminated with other halo pyrroles was available as the starting material; however, **262** was successfully isolated in ca. 50% yield.



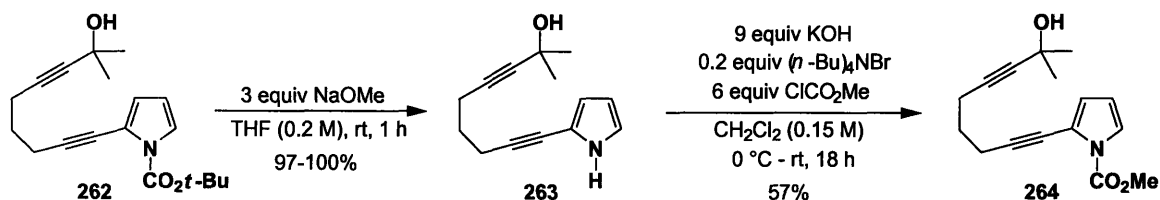
With **262** in hand, the simultaneous removal of both protecting groups was examined under the conditions outlined below.



Although cleavage of the *N*-Boc protecting group readily occurred in all cases even without heating, deprotection of the alkyne required much higher temperature.

The last two reaction conditions shown above seemed promising in small scale screening experiments; however, when the reaction was performed at half-gram scale in refluxing toluene, a complex mixture of products was obtained, presumably because the free pyrrole does not survive strongly basic conditions at high temperature. Therefore, this route was also abandoned.

The sequential removal of the *N*-Boc and alkyne protecting groups was then attempted. As mentioned above, the *N*-Boc group is readily removed under basic conditions, and this cleavage was found to occur in nearly quantitative yield on both small and large scale. Protection of the pyrrole as a methyl carbamate was then attempted, in order to allow for the deprotection of the alkyne under basic conditions at elevated temperature. A survey of the literature revealed phase transfer catalysis¹⁰⁰ as a mild and efficient method to accomplish this transformation, and this approach yielded the desired product in good yield as shown below.¹⁰¹

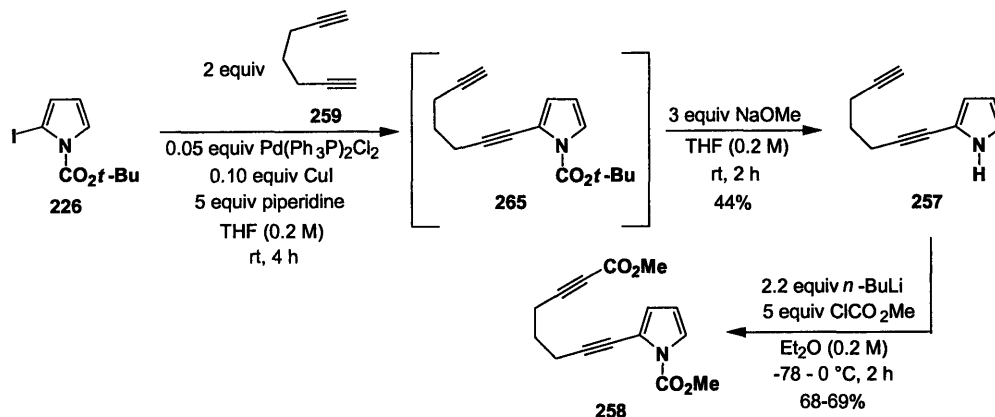


Unfortunately, subjecting the tertiary alcohol **264** to basic conditions (4 equiv *KOt*-Bu, THF, reflux) on a small scale (ca. 30 mg), led to simultaneous loss of the carbomethoxy protecting group. Subjecting **263** to the same conditions gave a complex mixture of product as described above for **262**, so this route was also abandoned.

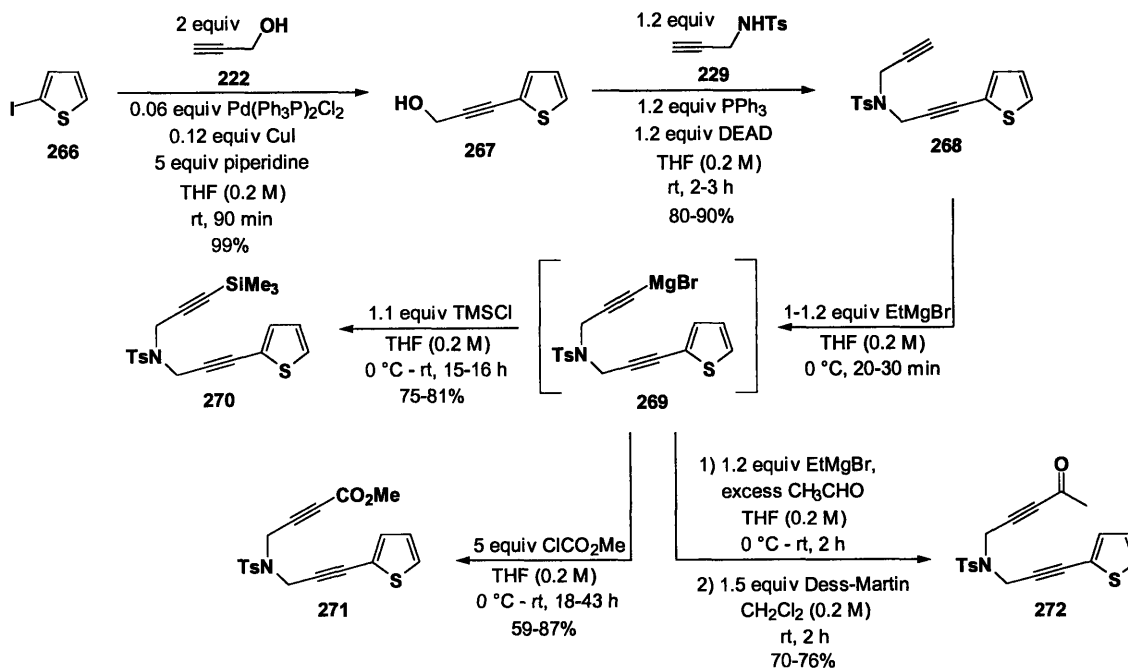
¹⁰⁰ For reviews, see: (a) Fiamegos, Y. C.; Stalikas, C. D. *Analytica Chimica Acta* **2005**, *550*, 1. (b) *Handbook of Phase-Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional: London, 1997. (c) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis*; Chapman & Hall: New York, 1994. (d) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; VCH: Weinheim, 1993.

¹⁰¹ Procedure based on conditions described by: Basaric, N.; Marinic, Z.; Sindler-Kulyk, M. *J. Org. Chem.* **2003**, *68*, 7524.

A second and more efficient route to **257** was finally accomplished by using the direct Sonogashira coupling of 2-iodo-*N*-Boc-pyrrole (**226**) with 1,6-heptadiyne (**259**), in a fashion analogous to that reported for 2-iodothiophene and 1,7-octadiyne.¹⁰² Double metalation of **257** with *n*-BuLi followed by reaction with methyl chloroformate then furnished alkynyl ester **258** in good yield.



A similar series of 2-tethered thiophene cycloaddition substrates was synthesized starting with commercially available 2-iodothiophene (**266**) as shown below.



¹⁰² Hay, C.; Hissler, M.; Fischmeister, C.; Rault-Berthelot, J.; Toupet, L.; Nyulászi, L.; Réau, R. *Chem. Eur. J.* **2001**, *7*, 4222.

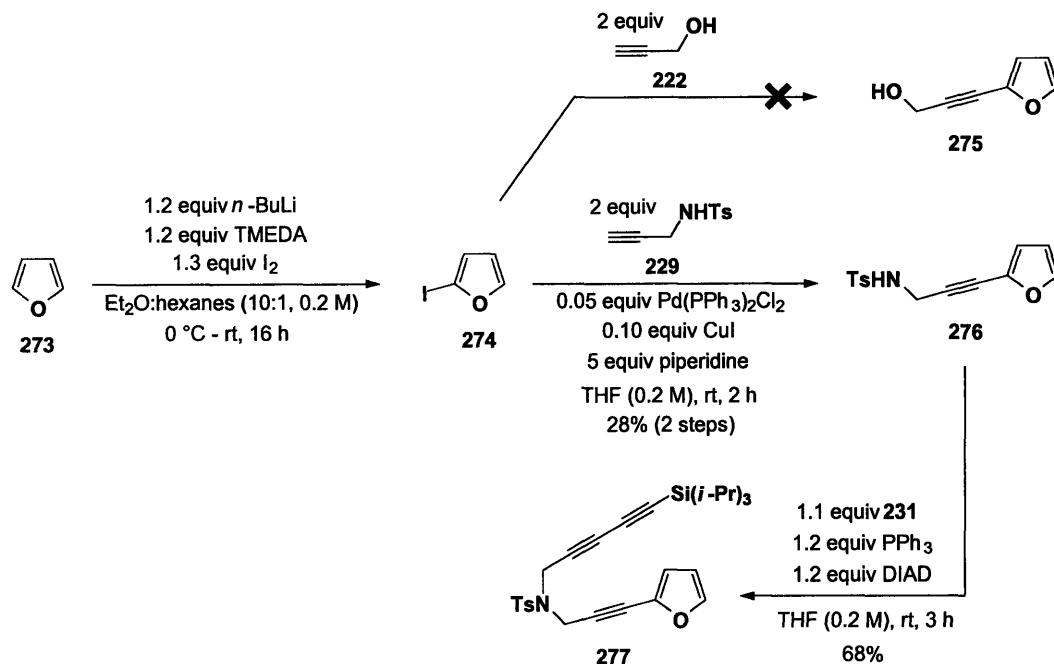
Thus, Sonogashira coupling of 2-iodothiophene with propargyl alcohol followed by Mitsunobu coupling of the resulting propargylic alcohol **267** with sulfonamide **229** gave terminal alkyne **268**. Metalation of this alkyne with EtMgBr then allowed for the creation of a library of substrates bearing different groups attached to the 2π component.

The synthesis of a similar series of furan derivatives was attempted by carrying out directed metalation of furan¹⁰³ in the presence of TMEDA followed by addition of I₂ to give 2-iodofuran (**274**). This iodide was then used without purification in Sonogashira couplings with propargyl alcohol and with sulfonamide **229**. Unfortunately, all attempts to purify propargylic alcohol **275**¹⁰⁴ were unsuccessful and the use of impure material in subsequent steps led to low yields of the desired products. A similar situation arose when attempting to build 3-tethered furans from 3-iodofuran¹⁰⁵ and propargyl alcohol. On the other hand, purification of propargylic sulfonamide **276** provided clean material that was successfully coupled via a Mitsunobu reaction with diynol **231**, furnishing diynyl furan **277**. The low yield of sulfonamide **276** was attributed to the use of impure 2-iodofuran, which like its pyrrole counterpart, is difficult to handle due to instability.⁸⁶

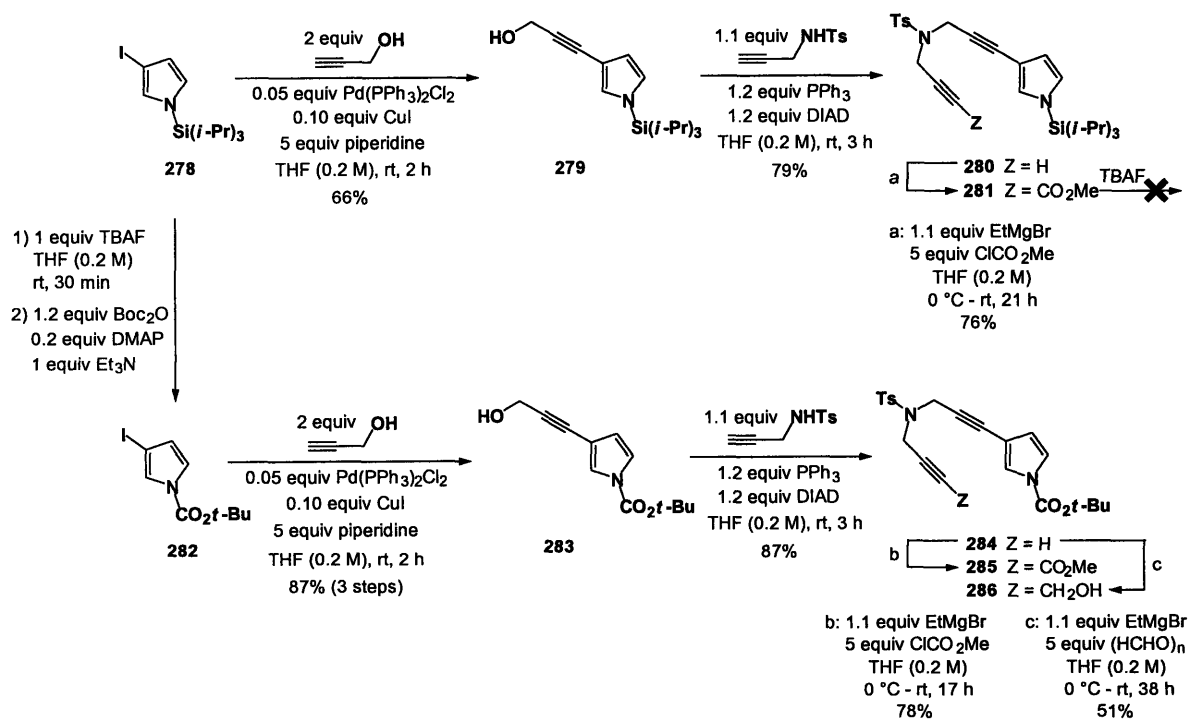
¹⁰³ (a) Gilman, H.; Shirley, D. A. *Tetrahedron Lett.* **1949**, 71, 1870. (b) Zeni, G.; Lüdtkke, D. S.; Nogueira, C. W.; Panatieri, R. B.; Braga, A. L.; Silveira, C. C.; Stefani, H. A.; Rocha, J. B. T. *Tetrahedron Lett.* **2001**, 42, 8927.

¹⁰⁴ Previously reported as the product of the Sonogashira coupling of propargyl alcohol with furyltellurium compounds. See: (a) Gilson Zeni, G.; Lüdtkke, D. S.; Nogueira, C. W.; Panatieri, R. B.; Braga, A. L.; Silveira, C. C.; Stefani, H. A.; Rocha, J. B. T. *Tetrahedron Lett.* **2001**, 42, 8927 (84%). (b) Braga, A. L.; Lüdtkke, D. S.; Vargas, F.; Donato, R. K.; Silveira, C. C.; Stefani, H. A.; Zeni, G. *Tetrahedron Lett.* **2003**, 44, 1779 (83%).

¹⁰⁵ Prepared from commercially available 3-bromofuran via metal-halogen exchange with *n*-BuLi followed by iodination with elemental iodine.



The synthesis of the 3-tethered pyrrole cycloaddition substrates 281, 285, and 286 was accomplished beginning with 3-iodo-*N*-(triisopropylsilyl)pyrrole (278)¹⁰⁶ as the starting material as shown below.



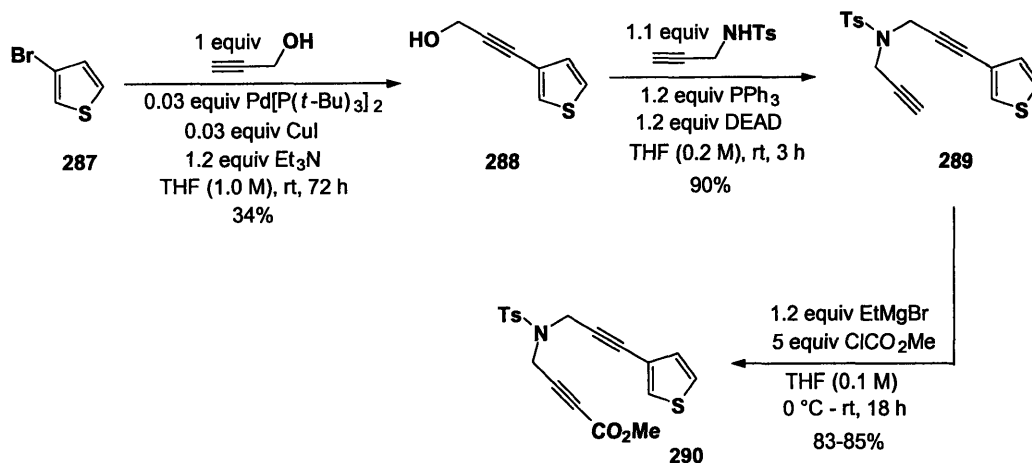
¹⁰⁶ Alvarez, A.; Guzmán, A.; Ruiz, A.; Velarde E. *J. Org. Chem.* **1992**, *57*, 1653.

The same reaction sequence of Sonogashira and Mitsunobu couplings with propargyl alcohol and sulfonamide **229**, respectively, gave the terminal alkyne **280**. Metalation of the alkyne with EtMgBr followed by reaction with methyl chloroformate gave alkynyl ester **281**. However, attempted desilylation of this silylpyrrole with TBAF led to its immediate and total decomposition. Therefore, exchange of TIPS for Boc was performed at an earlier stage by treating 3-iodo-*N*-(triisopropylsilyl)pyrrole with TBAF, and then treating the resulting 3-iodopyrrole (without purification) with di-*t*-butyl-dicarbonate in the presence of DMAP and triethylamine. This reaction furnished 3-iodo-*N*-(*t*-butoxycarbonyl)pyrrole (**282**) which carried a desilylation by-product that disappeared upon subjecting the mixture to the standard sequence of Sonogashira and Mitsunobu reactions. Metalation followed by reaction with ethyl chloroformate and paraformaldehyde furnished ester **285** and alcohol **286**, respectively, each in five steps overall from **278**.

The 3-tethered thiophene cycloaddition substrate **290** was synthesized starting with commercially available 3-bromothiophene (**287**) as shown below. Subjecting **287** to the same Sonogashira conditions previously used with all other substrates did not furnish any of the desired propargylic alcohol **288**.¹⁰⁷ However, the use of an alternate catalyst provided by the Fu group known to be more suitable for the alkynylation of aryl bromides¹⁰⁸ provided propargylic alcohol **288**, albeit in low yield. The low yield was attributed to the low reactivity of the heteraryl bromide in the reaction, but since enough material was obtained to proceed, no optimization of this coupling reaction was carried out. The assembly of **290** was then accomplished as described previously for the other substrates discussed above.

¹⁰⁷ Recently prepared in 55% yield via Sonogashira coupling of 3-bromothiophene and propargyl alcohol using a tetraphosphine palladium catalyst. See: Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2005**, *46*, 1717.

¹⁰⁸ Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729.

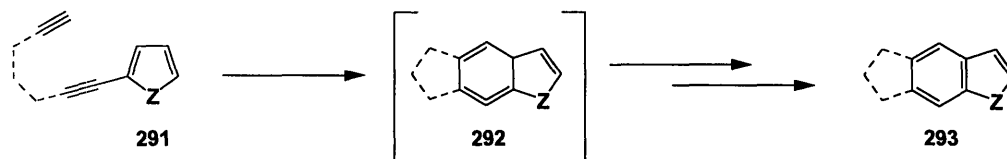


With all of these cycloaddition substrates in hand, a systematic investigation was begun of the reaction conditions that would allow for the efficient intramolecular cycloaddition of these compounds to furnish benzo[b]-fused five-membered hetarenes. The next chapter describes the cycloaddition experiments that were performed with these substrates, as well as the conclusions that can be inferred from the results of these experiments.

Chapter 2. Hetarenyne Cycloadditions

2.1. Cycloadditions of Vinyl Arenes and Hetarenes

The “hetarenyne cycloadditions” that were the focus of our studies require the disruption of the aromaticity of a heteroaromatic ring as illustrated in the prototypical transformation outlined below.



In considering the development of optimal conditions for effecting these reactions, it was therefore of interest to review the conditions typically employed in the somewhat related *Diels-Alder cycloadditions* of *alkenyl*-substituted heterocycles (vinyl hetarenes).¹⁰⁹ This section summarizes some of the literature in this area prior to the outset of our work.

The participation of styrenes as diene components in Diels-Alder reactions is a well known process.^{110,111} Because of the loss of aromaticity in the cycloaddition step, elevated temperatures are sometimes required for intermolecular reactions,¹¹² often leading to undesired by-products, polymerization, or decomposition. However, the cycloaddition can proceed under milder conditions when: (a) very reactive dienophiles are used,¹¹³ (b) the aromaticity of styrene is altered by coordination to certain transition

¹⁰⁹ (a) Thomas, E. J., Ed. *Science of Synthesis*; Georg Thieme Verlag: Stuttgart, Germany, 2001; Vol 10, pp 60-62 and 474-476.

¹¹⁰ For reviews, see: (a) Wagner-Jauregg, T. *Synthesis* **1980**, 769. (b) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; John Wiley & Sons: New York, 1990, Ch. 4.

¹¹¹ (a) Klemm, L. H.; McGuire, T. M.; Gopinath, K. W. *J. Org. Chem.* **1976**, *41*, 2571. (b) Klemm, L. H.; McGuire, T. M.; Gopinath, K. W. *J. Org. Chem.* **1976**, *41*, 3813.

¹¹² Rosen, B. I.; Weber, W. P. *J. Org. Chem.* **1977**, *42*, 3463.

¹¹³ (a) Hall, Jr., H. K.; Nogues, P.; Rhoades, J. W.; Sentman, R. C.; Detar, M. *J. Org. Chem.* **1982**, *47*, 1451. (b) Palenic, G. J. *J. Org. Chem.* **1985**, *50*, 4378.

metals,¹¹⁴ (c) Lewis acids catalysts¹¹⁵ are used, (d) the reaction is done under high-pressure,¹¹⁶ or (e) the vinyl group has a heteroatom substituent.¹¹⁷ The entropic advantage associated with intramolecular processes also allows for more facile Diels-Alder reactions with styrenes serving as 4π components.¹¹⁸ The typical conditions for [4+2] cycloadditions of styrenes serving as dienes with highly reactive dienophiles involve heating to reflux a solution of the diene and dienophile in a solvent like benzene (bp 80 °C), toluene (bp 110 °C), or xylene (bp 140 °C), the choice of which depends on the nature of the styrene, the dienophile, and any special reagents or conditions used, as mentioned above.

As briefly discussed in Part I, Section 1.5.4, very few examples of intramolecular cycloadditions of vinyl heteroarenes are known, so most data currently available pertains to intermolecular reactions.¹⁰⁹ Vinylpyrroles¹¹⁹ and vinylfurans are relatively unstable, being prone to cationic polymerization. In the presence of highly electrophilic dienophiles, electrophilic aromatic substitution can compete with cycloaddition, a side reaction that in pyrroles can be suppressed by deactivation using electron-withdrawing substituents on the nitrogen. Note, however, that bulky substituents on the nitrogen such as phenyl can increase the ratio of substitution relative to cycloaddition.¹²⁰ With vinylfurans there can also be competition with the furan itself acting as a diene, but this can be modulated by introducing electron-withdrawing groups on the ring¹²¹ or by

¹¹⁴ Kolis, S. P.; Chordia, M. D.; Liu, R.; Kopach, M. E.; Harman, W. D. *J. Am. Chem. Soc.* **1998**, *120*, 2218.

¹¹⁵ Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch Jr., K. O.; Ray, J. E. *J. Org. Chem.* **1994**, *59*, 6567.

¹¹⁶ Carreño, M. C.; Mahugo, J.; Urbano, A. *Tetrahedron Lett.* **1997**, *38*, 3047.

¹¹⁷ Willmore, N. D.; Hoic, D. A.; Katz, T. J. *J. Org. Chem.* **1994**, *59*, 1889.

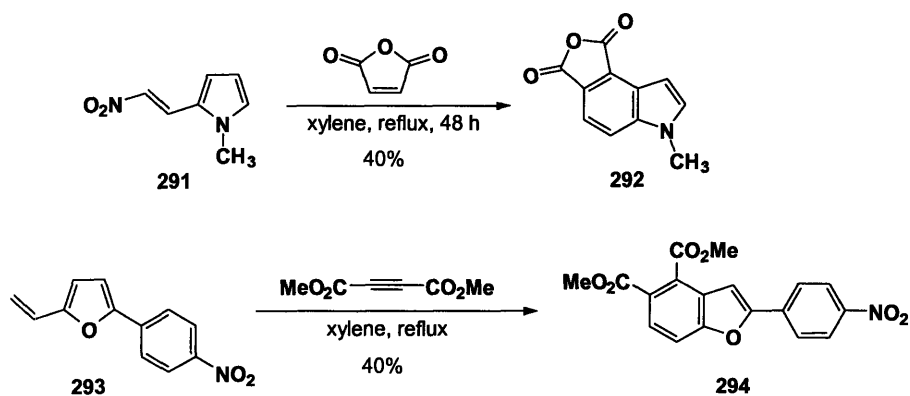
¹¹⁸ (a) Dawson, J. R.; Mellor, J. M.; *Tetrahedron Lett.* **1995**, *36*, 9043. (b) Sun, S.; Turchi, I. J.; Xu, D. Murray, W. V. *J. Org. Chem.* **2000**, *65*, 2555. (c) Pedrosa, R.; Andrés, C.; Nieto, J. *J. Org. Chem.* **2002**, *67*, 782

¹¹⁹ For a review of the use of vinyl pyrroles as synthetic building blocks, including examples of [4+2] cycloadditions, see reference 109 and Trofimov, B. A.; Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. I. *Chem. Rev.* **2004**, *104*, 2481.

¹²⁰ Jones, R. A.; Saliente, T. A.; Arques, J. S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2541.

¹²¹ Kusurkar, R. S.; Bhosale, D. K. *Synth. Commun.* **1990**, *20*, 101.

introducing an electron-donating atom on the vinyl moiety.¹²² Despite these drawbacks, reaction conditions and structural features in the substrates can often be tailored to favor the desired cycloaddition. Reaction of vinylpyrroles with alkynes gives dihydroindoles,¹²³ which can be easily dehydrogenated. When the vinyl moiety carries a potential leaving group, the aromatic indole can be accessed directly as in the transformation **291** → **292** below. In the case of vinyl heteroarenes where this feature is lacking, the aromatic product can also be obtained directly, presumably via disproportionation or air oxidation, as illustrated with the transformation **293** → **294**.



The typical conditions for cycloaddition of vinyl heteroarenes with dienophiles are not much different from the conditions used with vinyl arenes (styrenes), where the diene and dienophile are usually heated to reflux in a solution of a solvent like benzene, toluene, or xylene. Below are some examples.

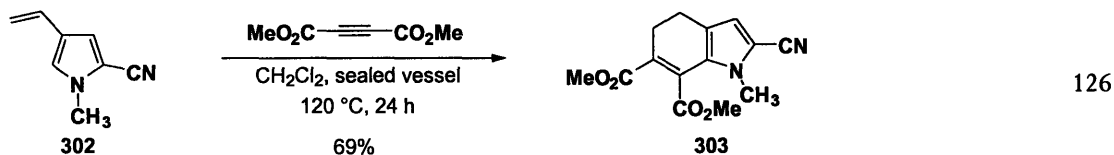
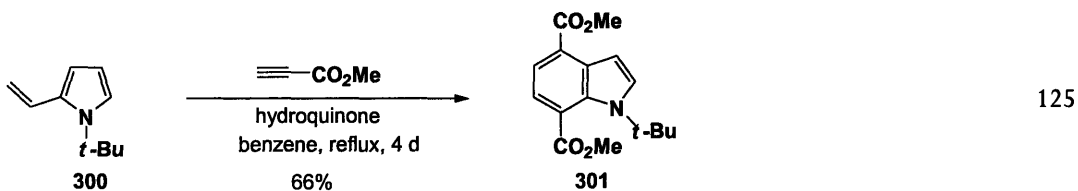


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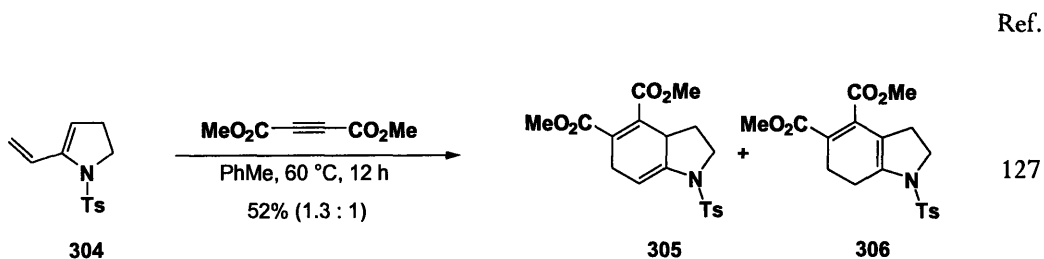
111

¹²² Benítez, A.; Herrera, F. R.; Romero, M.; Talamás, F. X.; Muchowski, J. M. *J. Org. Chem.* **1996**, *61*, 1487.

¹²³ See reference 1a and Jones, R. A.; Arques, J. S. *Tetrahedron* **1981**, *37*, 1597.



The typical conditions for Diels-Alder reactions involving related non-aromatic dienes are generally milder, since loss of aromaticity is not an issue, as shown in the example below.



Based on the data presented in this section, as well as previous experience with enyne cycloadditions in the Danheiser group, it seemed appropriate to begin examining the heteroenyne cycloaddition by heating substrates in a solution of benzene or toluene, at or around reflux temperatures (i.e., 80-110 °C), using 1-3 equivalents of a phenolic compound as an additive. The entropic advantage of the intramolecular reaction should

¹²⁴ Muchovski, J. M.; Scheller, M. E. *Tetrahedron Lett.* **1987**, *28*, 3453.

¹²⁵ Jones, R. A.; Marriott, M. T. P.; Rosenthal, W. P.; Arques, J. S. *J. Org. Chem.* **1980**, *45*, 4515. This example involves initial cycloaddition followed by rearomatization of the pyrrole moiety. The resulting bicyclic 3-vinylpyrrole undergoes a second cycloaddition with another alkyne, followed by cycloreversion with loss of ethylene.

¹²⁶ Gonzales-Rosende, E.; Jones, R. A.; Sepulveda-Arques, J. S. *Synth. Commun.* **1988**, *18*, 1669.

¹²⁷ Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803.

assist in facilitating the reaction, so relatively mild conditions were expected to yield the desired cycloadducts. The pages that follow describe in detail the hetarenyne cycloaddition chemistry that was developed as part of the ongoing research in the Danheiser group.

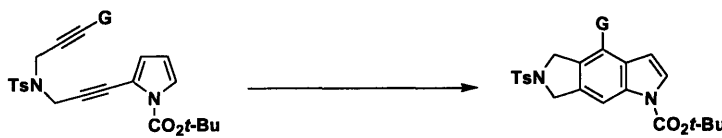
2.2. Effects of Substrate Structure on the Facility of Hetarenyne Cycloadditions

In accordance with the objectives of the project, the scope of the cycloaddition chemistry was studied with respect to four major variations in the structure of the substrates: (a) type of activating groups attached to the 2π component, (b) composition of the tether, (c) attachment position of the tether on the hetarene, and (d) the nature of the hetarene (i.e., pyrrole, thiophene, or furan). This section presents the results of this systematic investigation. Sections 2.3 and 2.4 then describe our findings with regard to the use of phenolic additives and alcohols as solvents, as well the possibility of effecting the reaction under mild conditions by the use of Lewis acids. Finally, Section 2.5 presents quantitative rate data for two series of related cycloaddition reactions. As detailed in the sections that follow, thermal cycloadditions were generally performed in a solution of benzene or toluene, usually in the presence of BHT (see Section 2.4 of Part I for a mechanistic discussion of the role of BHT), and under conditions of relatively high dilution (0.05 M) to minimize intermolecular processes and thus favor the intramolecular cycloaddition. Reactions requiring temperatures above refluxing toluene (bp 110 °C) were performed in degassed solutions in “resealable” tubes sealed with a threaded Teflon cap.

2.2.1. Activating Groups Attached to the 2 π Component

The table below presents our results with various pyrrole cycloaddition substrates that explore the effect of the activating group attached to the 2 π component on the facility of cycloaddition.

Table 1. Cycloaddition of 2-Tethered Alkynyl Pyrroles

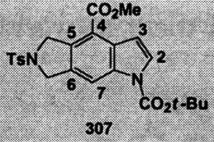
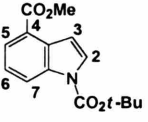
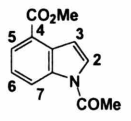
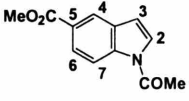
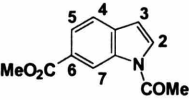
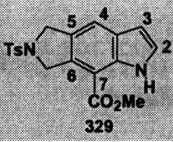
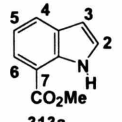
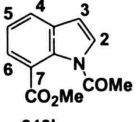


substrate	G	conditions	cycloadduct	isolated yield (%)
243	CO ₂ Me	3 equiv BHT benzene reflux, 15 h	307	57
244	CH ₂ OH	1.5 equiv Dess-Martin CH ₂ Cl ₂ rt, 30 h	308 (G = CHO)	58
245	PO(OEt) ₂	3 equiv BHT toluene 130 °C, 6 h	309	61
232	C≡CSi(<i>i</i> -Pr) ₃	3 equiv BHT benzene reflux, 2 h	310	48

Small scale screening experiments performed with pyrrole cycloaddition substrate **243** bearing an alkynyl ester as the 2 π component revealed the cycloaddition reaction was complete within one hour at 110 °C. As shown in Table 1, when the cycloaddition of **243** was performed in a preparative scale by heating in refluxing benzene in the presence of BHT, indole **307** was obtained in 57% yield. The structural assignment of **307** was made by comparing its ¹H-NMR spectral data with that of related compounds previously reported in the literature. Table 2 below shows the data used to determine the structures of **307** and **329** (see Section 2.2.3 for its synthesis); all other structures in our investigations were established by comparison with the data for **307** and **329**.¹²⁸

¹²⁸ Spectral data for reference compounds obtained from: (a) Kasahara, A.; Izumi, T.; Murakami, S.; Miyamoto, K.; Hino, T. *J. Heterocycl. Chem.* **1989**, *26*, 1405. (b) Fauq, A. H.; Hong, F.; Cusack, B.; Tyler, B. M.; Ping-

Table 2. Comparison of ¹H-NMR Data for Various Carbomethoxyindoles

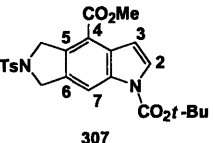
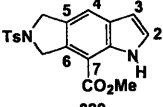
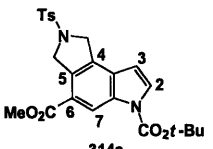
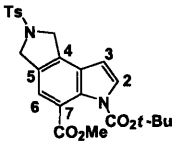
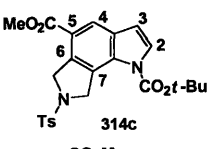
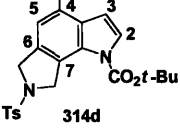
Ref.	Structure	Chemical Shift (ppm) in CDCl ₃					
		H-2	H-3	H-4	H-5	H6	H-7
	 307	7.62	7.16	-	-	-	8.21
128b	 311a	7.71	7.28	-	7.98	7.36	8.41
128a	 311b	7.47	7.31	-	7.96	7.36	8.65
128a	 312a	7.42	6.63	8.82	-	7.96	8.40
128a	 312b	7.55	6.61	7.53	7.83	-	9.03
	 329	~7.25	6.50	7.56	-	-	-
128a	 313a	7.17	6.54	~7.8	7.06	~7.8	-
128a	 313b	~7.3	6.67	7.54	~7.3	7.67	-

The alternate structures shown in Table 3 below can be conceived as products of the cycloaddition of **243** or **285** (*vide infra*) if unexpected rearrangements had occurred

Pang, Y.; Richelson, E. *Tetrahedron: Asymmetry* **1998**, 9, 4127. See also (c) reference 84, (d) de Koning, C. B.; Michael, J. P.; Rousseau, A. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1705, and (e) Liao, J.; Chen, C.; Chou, H.; Cheng, C.; Chou, P.; Fang, J.; Slanina, Z.; Chow, T. *J. Org. Lett.* **2002**, 4, 3107.

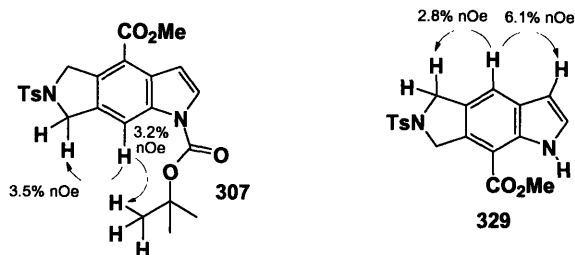
during the cycloaddition. Based on the data in Table 2, one can predict the chemical shifts of the indole protons in these alternate structures, as shown in Table 3. Although these predicted chemical shifts do not perfectly match the experimental data for **307** and **329**, there was enough similarity between some of them to warrant further studies to confirm the structures of cycloadducts **307** and **329**.

Table 3. Comparison of the Predicted Chemical Shifts of Alternate Structures with **307** and **329**.

Structure	indole δ (ppm) in CDCl ₃
 <p>307</p>	8.21 (H-7), 7.62 (H-2), 7.16 (H-3) (experimental)
 <p>329</p>	7.56 (H-4), 7.25 (H-2), 6.50 (H-3) (experimental)
 <p>314a</p>	9.0 (H-7), 7.6 (H-2), 6.6 (H-3) (predicted)
 <p>314b</p>	7.7 (H-6), 7.2 (H-2), 6.7 (H-3) (predicted)
 <p>314c</p>	8.8 (H-4), 7.4 (H-2), 6.6 (H-3) (predicted)
 <p>314d</p>	8.0 (H-5), 7.7 (H-2), 7.3 (H-3) (predicted)

Thus, to absolutely confirm the structures of **307** and **329**, nOe experiments were conducted. For **307**, upon irradiation of H-7 there was a 3.5% enhancement in the signal of the methylene attached to C-7 of the indole ring simultaneous with a 3.2%

enhancement of the signal of the Boc group. For **329**, irradiation of H-4, led to a 2.8% enhancement of the signal of the methylene attached to C-6 of the indole ring and also a 6.1% enhancement of the signal of the C-3 proton of the indole. These experiments unequivocally established the structures of these compounds.



As Table 1 shows, substituting a formyl group for the ester moiety leads to an even more reactive substrate, since isolation of the uncyclized aldehyde from the Dess-Martin oxidation of alcohol **244** was not possible, and the cycloadduct **308** was isolated directly from the oxidation reaction. This fact that an aldehyde is a much better activating group than the corresponding ester in [4+2] cycloadditions is well documented.¹²⁹ The higher electron-withdrawing character of aldehydes has a stronger effect on the lowering of the energy of the LUMO of the 2π component, leading to a more facile reaction.

On the other hand, as seen in Table 1, cycloaddition of phosphonate **245** required higher temperatures. The Diels-Alder cycloaddition of vinylphosphonates and 1,3-dienes has not been exploited, and the few reported examples are limited to the synthesis of monophosphonate cyclohexenes.¹³⁰ Vinylphosphonates are much less reactive as dienophiles than α,β -unsaturated carbonyl compounds,^{130,131,132} although their

¹²⁹ For studies of intramolecular Diels-Alder reactions comparing aldehydes and esters as activating groups for 2π components, see: Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236, and references cited therein.

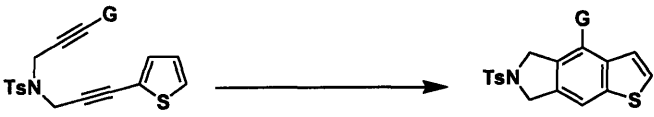
¹³⁰ Daniewski, W. M.; Griffin, C. E. *J. Org. Chem.* **1966**, *31*, 3236.

¹³¹ McClure, C. K.; Hansen, K. B. *Tetrahedron Lett.* **1996**, *37*, 2149.

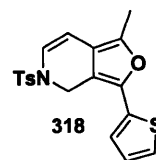
reactivity can be greatly enhanced in the presence of Lewis acids¹³¹ or by introduction of a second electron-withdrawing substituent around the carbon-carbon double bond.^{131,132}

Interestingly, diyne **232** is more reactive than the corresponding ester, although not as reactive as the aldehyde. Previous studies in our laboratory had demonstrated this phenomenon,^{5b,c} and it is believed that the magnitude of the electronegativity of the sp-hybridized carbons in an alkyne allows for an inductive effect that is comparable to the effect exerted by EWGs like carbonyl groups and thus is sufficiently high to activate the 2π component in a similar fashion. The lower yield of cycloadduct **310** could be the result of thermal instability of the product, as suggested by the results of kinetic experiments performed with diyne **232** (see Section 2.5 of this chapter).

Table 4. Cycloaddition of 2-Tethered Alkynyl Thiophenes



substrate	G	conditions	cycloadduct	isolated yield (%)
270	SiMe ₃	3 equiv BHT toluene 150 °C, 44 h	315	80
271	CO ₂ Me	2 equiv BHT toluene reflux, 6 h	316	70
272	COMe	3 equiv BHT toluene 150 °C, 17 h	317	41



As shown in Table 4, a comparable trend in reactivity of the 2π component was observed in alkynyl thiophenes. All attempts to perform the cycloaddition with a terminal alkyne as the 2π component (i.e., G = H) were unsuccessful and led either to

¹³² Defacqz, N.; Touillaux, R.; Tinant, B.; Declercq, J.-P.; Peeters, D.; Marchand-Brynaert, J. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1965.

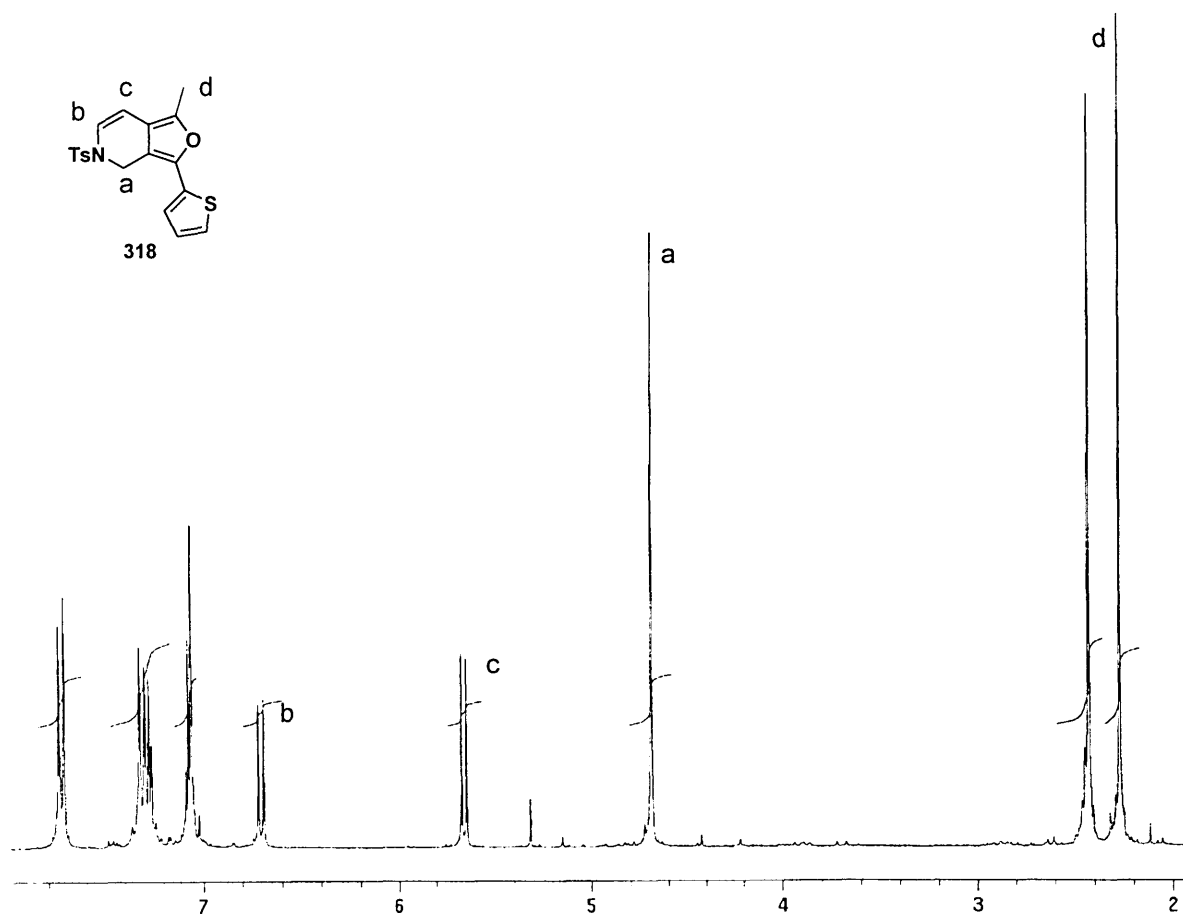
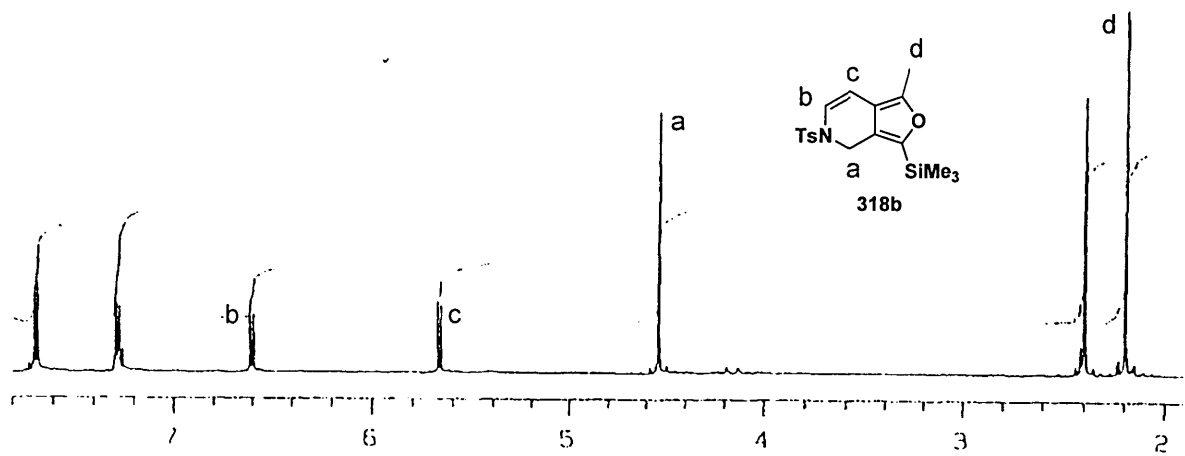
no reaction ($T < 200\text{ }^{\circ}\text{C}$) or decomposition ($T > 200\text{ }^{\circ}\text{C}$). As an equivalent for the terminal alkyne, the trimethylsilylacetylene **270** was subjected to the reaction and smooth cycloaddition was observed at $150\text{ }^{\circ}\text{C}$ to furnish benzo[b]thiophene **315** in very good yield. When attempting a cycloaddition of an alkynylsilane with an alkynylpyrrole substrate, no reaction was observed below $150\text{ }^{\circ}\text{C}$, and decomposition resulted when heating above this temperature. The observed instability is believed to result from thermolysis of the Boc group (*vide infra*), which leaves the pyrrole unprotected and presumably leads to its destruction at the elevated temperature. The cycloaddition of alkynyl silane **270** was subsequently found to actually be complete at $150\text{ }^{\circ}\text{C}$ in only ca. 24 h, indicating that benzothiophene **315** is quite stable under the reaction conditions.

As expected, the alkynyl ester **271** was more reactive than the alkynylsilane. Heating a toluene solution of **271** to reflux (bp $110\text{ }^{\circ}\text{C}$) for 6 h in the presence of two equivalents of BHT furnished the desired benzo[b]thiophene **316** in 70% yield. However, when the alkynyl ketone **272** was subjected to the cycloaddition reaction conditions, two products resulted, **317** (41%) and **318** (ca. 20%). By-product **318** results from the [4+2] heteroenyne cycloaddition¹³³ of the alkynyl ketone with the thienyl alkyne acting as the 2π component, a transformation that was previously found not to occur with alkynyl esters.^{5b,6c} Although this potential side reaction was originally considered as a possible complication, the reactivity of the alkynyl thiophene as a 4π component was expected to be higher than that of the ynone. The assignment of the structure of **318** was easily made by comparison of its $^1\text{H-NMR}$ spectral data with that of a related cycloadduct (**318b**) previously prepared in the group, as shown below.^{5b,6c}

The chemical shifts of the tosyl, methylene (a), furylmethyl (d), and vinyl protons (b and c) of **318** and **318b** are nearly identical, as are the relative coupling constants for

¹³³ See Part I, Chapter 2, section 2.5 (above) and reference 5b.

the vinyl and tosyl protons. In addition, HRMS revealed a molecular mass of 394.0530, which is in agreement with the calculated value of 394.0542. With all this data, the proposed structure of **318** is believed to be correct one.

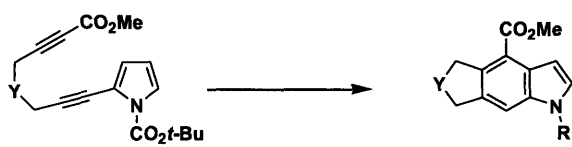


The experiments discussed above revealed a reactivity trend that is analogous to the substituent effects known for normal electron demand Diels-Alder reactions,¹³⁴ in which EWGs on the 2π component facilitate the reaction. However, based on the previous discussion of the possible mechanistic pathways for this transformation, the distinction between a concerted process and a stepwise radical pathway cannot be easily made. All the alkynyl 2π components described to this point are attached to electron-withdrawing substituents that are also good radical stabilizing groups (except the silyl group). Other experiments that will be presented in a later section will address this issue further.

2.2.2. Composition of the Tether

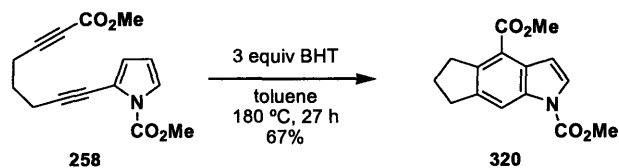
Changing the composition of the tether was demonstrated to have a significant effect on the ease of reaction. This effect had been seen before with enyne (unpublished results) and heteroenyne cycloadditions.^{5b} The following results illustrate these trends.

Table 5. Cycloaddition of Alkynyl Pyrroles with Tethers of Varying Composition

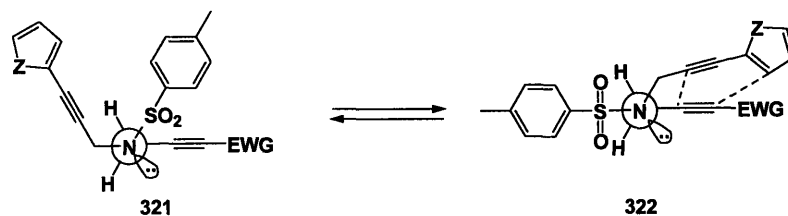


substrate	Y	conditions	cycloadduct	isolated yield (%)
243	NTs	3 equiv BHT benzene reflux, 15 h	307 (R = CO ₂ t-Bu)	57
251	S	3 equiv BHT toluene 180 °C, 5 h	319 (R = H)	46

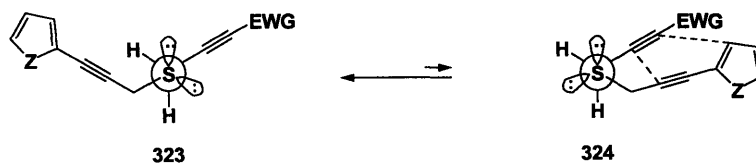
¹³⁴ For a discussion see: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: New York, 1996.



As seen in Table 5 above, replacing the sulfonamide nitrogen with a methylene has a dramatic effect on the facility of the reaction. This observation is believed to result from an alteration of two effects that are simultaneously operating in **243**: (1) the inductive electron-withdrawing effect of the sulfonamide nitrogen, which is believed to have an activating influence on the 2π component, and (2) the “Thorpe-Ingold effect”¹³⁵ associated with the large tosyl group attached to the nitrogen, which leads to an increase in the population of conformers (**322**) that are able to undergo cycloaddition.

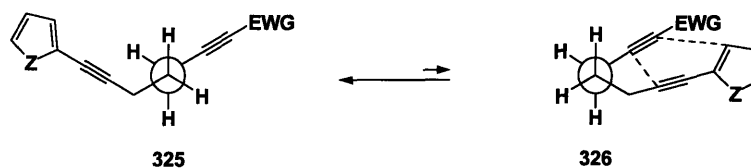


Replacing NTs with the less electronegative sulfur atom leads to a decrease in electron-withdrawing inductive effect within the tether, which is believed to result in a reduction in the activation of the 2π component. In the sulfur-tethered substrate there is also a relative increase in the population of conformers where the two alkyl chains attached to the heteroatom are *anti*, therefore reducing the proportion of molecules able to undergo cycloaddition.



¹³⁵ (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, 107,1080 (b) Ingold, C. K. *J. Chem. Soc.* **1921**, 119, 305. For a review, see: (c) Sammes, P. G.; Weller, D. J. *Synthesis* 1995, 1205.

Replacing the sulfur with a methylene group results in a further reduction of the electron-withdrawing inductive effects within the tether, which leads to an even less facile reaction, as can be seen by the longer reaction time at 180 °C (27 h) required for complete cycloaddition of **258** compared to the sulfide **251** (5 h).

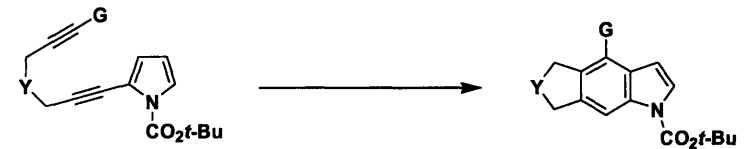


One potentially useful side-reaction that occurred with the sulfide substrate **251** was thermolysis of the Boc group. It is well known that Boc groups can be easily removed from indoles and pyrroles by heating either neat or in solution at temperatures above 150 °C,¹³⁶ and if cleavage of a Boc group is desired, it can be potentially carried out simultaneous with cycloaddition simply by heating the reaction mixture above 150 °C for a few hours. However, this may have an impact on the yield, particularly if the Boc thermolysis occurs faster than the cycloaddition, since having an unprotected pyrrole in the presence of a proton source like BHT at elevated temperatures could lead to decomposition.

As shown in Table 6, cycloaddition of aldehyde **254** with an all-carbon tether requires temperatures around 110 °C, in contrast to the related sulfonamide cycloaddition substrate which undergoes reaction at room temperature as soon as it is formed during oxidation of primary alcohol **244**.

¹³⁶ Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141

Table 6. Cycloadditions of Alkynyl Pyrroles with Alkynyl Aldehydes



substrate	Y	G	conditions	cycloadduct	isolated yield (%)
254	CH ₂	CHO	3 equiv BHT toluene reflux, 36 h	327	51
244	NTs	CH ₂ OH	1.5 equiv Dess-Martin CH ₂ Cl ₂ rt, 30 h	308	58

2.2.3. Attachment Position of the Tether on the Hetarene

The position of attachment of the 2π component to the hetarenyne ring (C-2 vs. C-3) was also found to have an interesting effect on facility and efficiency of the cycloaddition. The data available from intermolecular Diels-Alder cycloadditions of 2- and 3-vinylpyrroles and vinylfurans does not show a clear difference in reactivity between these two systems (see Section 2.1 of this chapter). As shown in Table 7, when first studying the effects of varying the attachment position of the tether under thermal conditions, it was found that in the case of 3-tethered substrates the presence of BHT has a detrimental effect on the outcome of the reaction. An explanation for this observation is presented below in Section 2.3. The cycloaddition of 3-tethered thiophene substrate **290** was consequently run in the absence of BHT and the desired product **328** was obtained in 45% yield. Note that cycloaddition substrate **290** was thus found to be less reactive than the analogous substrate **271** differing in the position of the attachment of the tether. A similar trend of reactivity was observed with 2- and 3-tethered pyrrole cycloaddition substrates (Table 8), which suggests that these reactions may be proceeding via a stepwise pathway (*vide infra*). The effect of using Lewis acids to promote these reactions is discussed in Section 2.4 below.

Table 7. Cycloaddition of a 3-Tethered Alkynyl Thiophene with an Alkynyl Ester

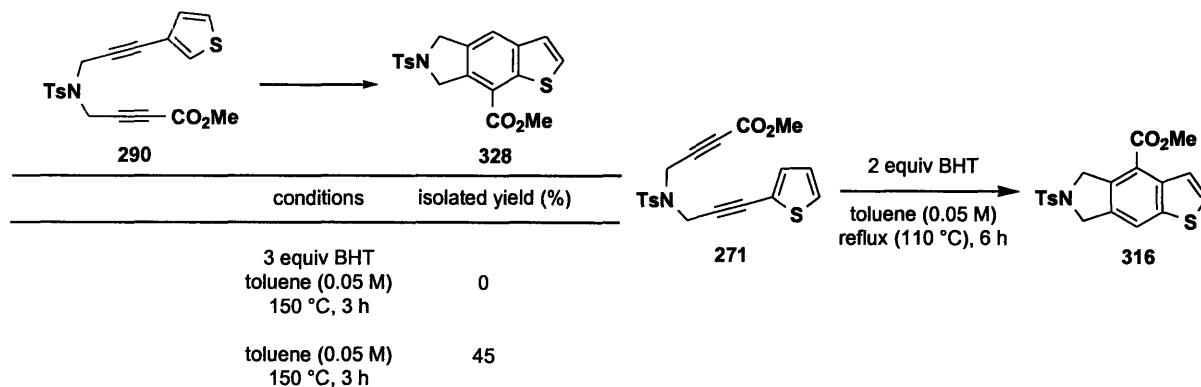
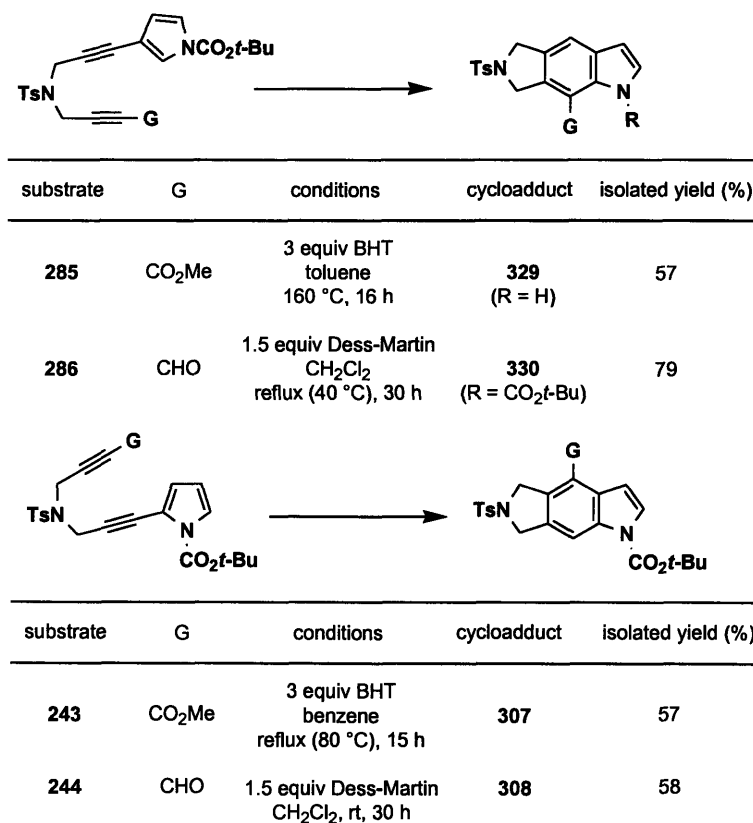
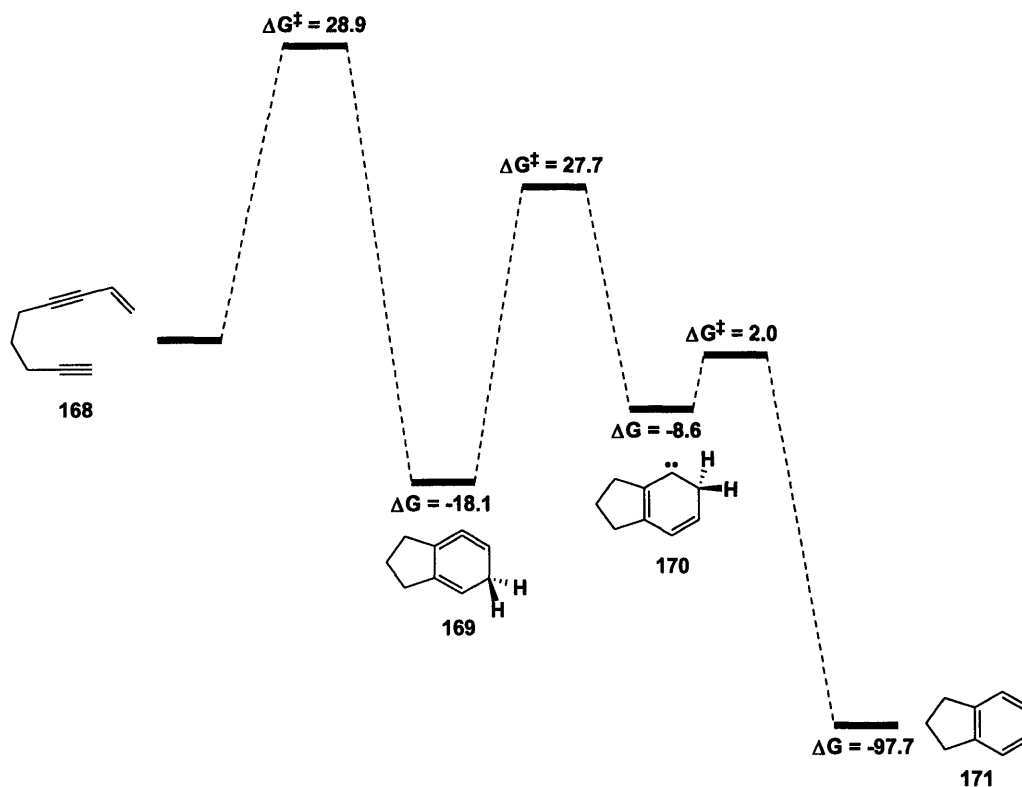


Table 8. Comparison of 3- and 2-Tethered Alkynyl Pyrrole Cycloadditions

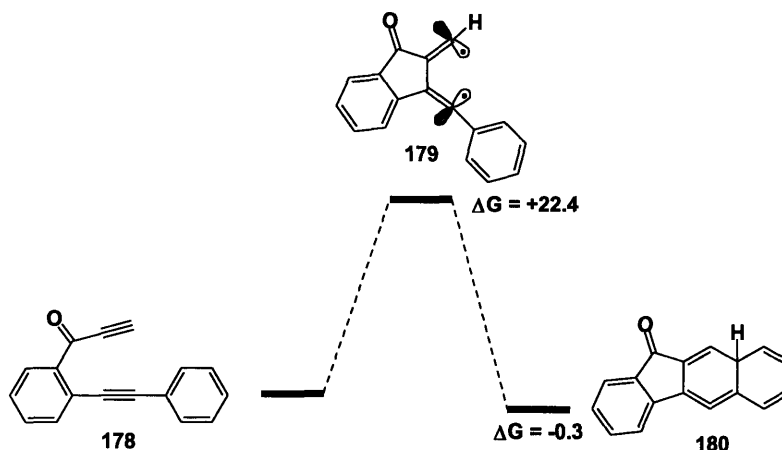


What follows is a possible explanation as to why the cycloaddition of 2-tethered substrates may be more facile than that of 3-tethered substrates. As discussed in Part I, Section 2.4 and shown below, calculations performed by Ananikov on generic enyne

cycloaddition substrate **168** predict that cyclic allene **169** is lower in energy than **168** by nearly 20 kcal/mol.



As also discussed in Part I, a computational study by Saá on the cycloaddition of arenynes **178** to form cyclic allene **180** compared concerted and stepwise pathways and found energy minima only for the stepwise mechanism. In this case there is a much smaller difference in relative free energy between the cycloaddition substrate **178** and the cyclic allene **180** presumably due to the disruption in the aromaticity of **178** during the transformation.



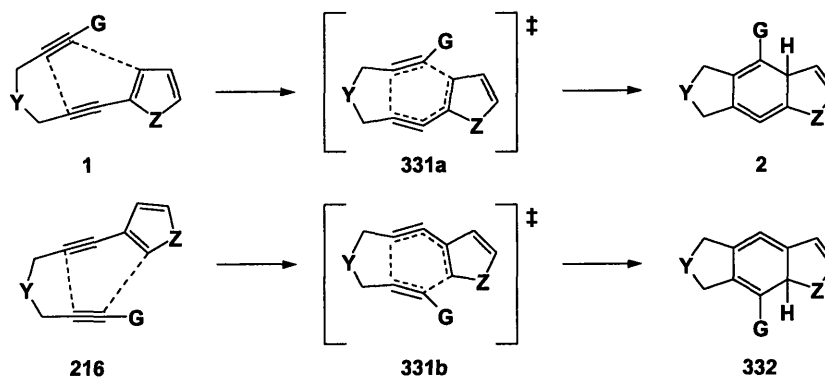
As with the formation of **180**, with the hetarenyne substrates there is a disruption in the aromaticity of the hetarene as the cyclization proceeds. However, hetarenes have a lower degree of aromaticity as compared to benzene. The magnitude of the difference in aromaticity between benzene and thiophene, pyrrole, and furan has been estimated by various methods,¹³⁷ two of which are shown in the table below.

	% aromaticity relative to benzene (bond lengths)	% aromaticity relative to benzene (resonance energy)
thiophene	45	81
pyrrole	37	60
furan	12	45

The lower degree of aromaticity of hetarenes compared to that of benzene may lead to the ΔG° for the hetarenyne cycloadditions **1** \rightarrow **2** and **216** \rightarrow **332** (see scheme below) being much more negative than that of the arenyne cycloaddition **178** \rightarrow **180**, although most likely not as negative as the -18.1 kcal/mol calculated for enyne cycloaddition **168** \rightarrow **171**. If this were to hold true, for a concerted cycloaddition the

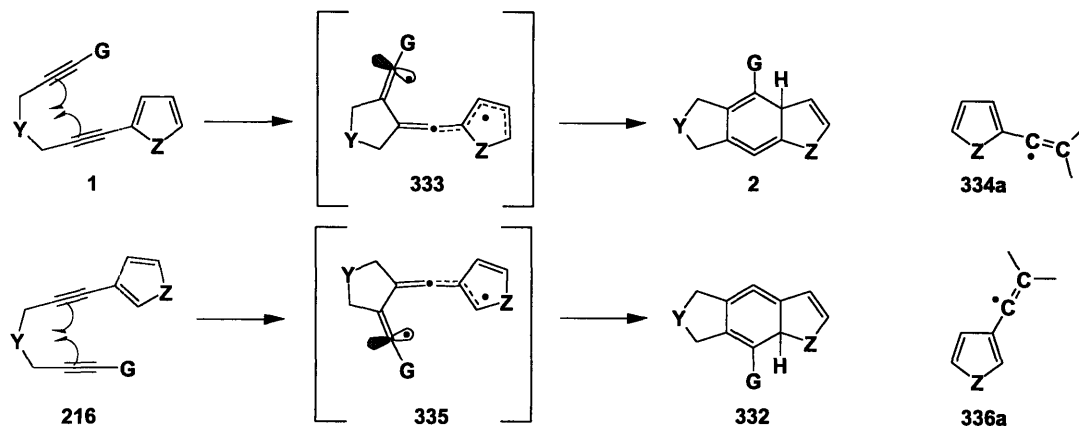
¹³⁷ Gilchrist, T. *Heterocyclic Chemistry*, 3rd ed.; Prentice Hall: Harlow, England, 1997, pp 17, 23.

difference in energy between the transition states **331a** and **331b** for the formation of the cyclic allene intermediates **2** and **332** would be influenced more by factors that affect the relative energy of **1** and **216** than by factors affecting the relative energy of the allenes **2** and **332**, in accordance with the Hammond postulate.¹³⁸ If there were no significant difference in the energy between generic cycloaddition substrates **1** and **216**, the concerted cycloaddition of **1** and **216** would have a small difference in rate. If, however, there is a significant difference in the energy of cycloaddition substrates **1** and **216**, this difference could lead to a measurable difference in the rate of cycloaddition even if the reaction were to proceed via a concerted pathway.

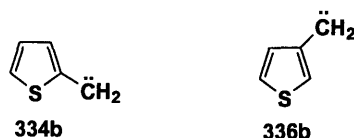


Now consider the heteroene cycloaddition proceeding via a stepwise pathway, with the rate-determining step being the initial cyclization leading to the high-energy biradical intermediate. Formation of biradical **333** from a 2-tethered cycloaddition substrate can be rationalized by a combination of radical stability⁶⁵ arguments and the Hammond postulate to proceed via a lower energy pathway than the formation of its less delocalized analog **335**.

¹³⁸ Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.



At first glance, analyzing the structure of biradical **333** suggests that it may enjoy greater electron delocalization than its 3-tethered analog **335**. A more rigorous analysis would require the determination of the relative stabilities of hetarylvinyl radicals like **334a** and **336a**. We could not find any literature reports on studies of the relative stability of hetarylvinyl radicals of this type, however, one recent computational study involving 2- and 3-thienylmethylene carbenes¹³⁹ revealed that the 2-thienylmethylene **334b** is more stable than the 3-thienylmethylene **336b** by 5 kcal/mol.

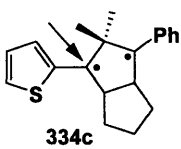
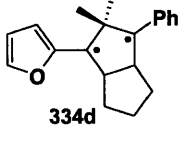
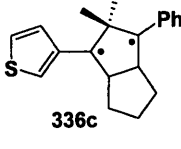
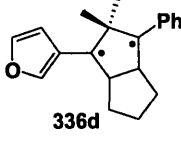


Another recent computational study looked at the ability of 2- and 3-thienyl and 2- and 3-furyl groups to delocalize electron spin density (*D*) of an adjacent radical center. The *lower the electron spin density* at the radical center, the *greater degree of delocalization* of the radical into the adjacent hetaryl group, which is correlated with *greater stability*. This study revealed that 2-hetaryl radicals are able to delocalize electron spin density better than the 3-hetaryl analogs at the pseudo-benzylic position.¹⁴⁰ As shown in the table below, the 2-hetaryl radicals **334c** and **334d** have a lower electron

¹³⁹ McKee, M. L.; Shevlin, P. B.; Zottola, M. J. *Am. Chem. Soc.* **2001**, *123*, 9418.

¹⁴⁰ Adam, W.; Emmert, O.; Harrer, H. M. *J. Chem. Soc., Perkin Trans. 2* **1997**, *4*, 687.

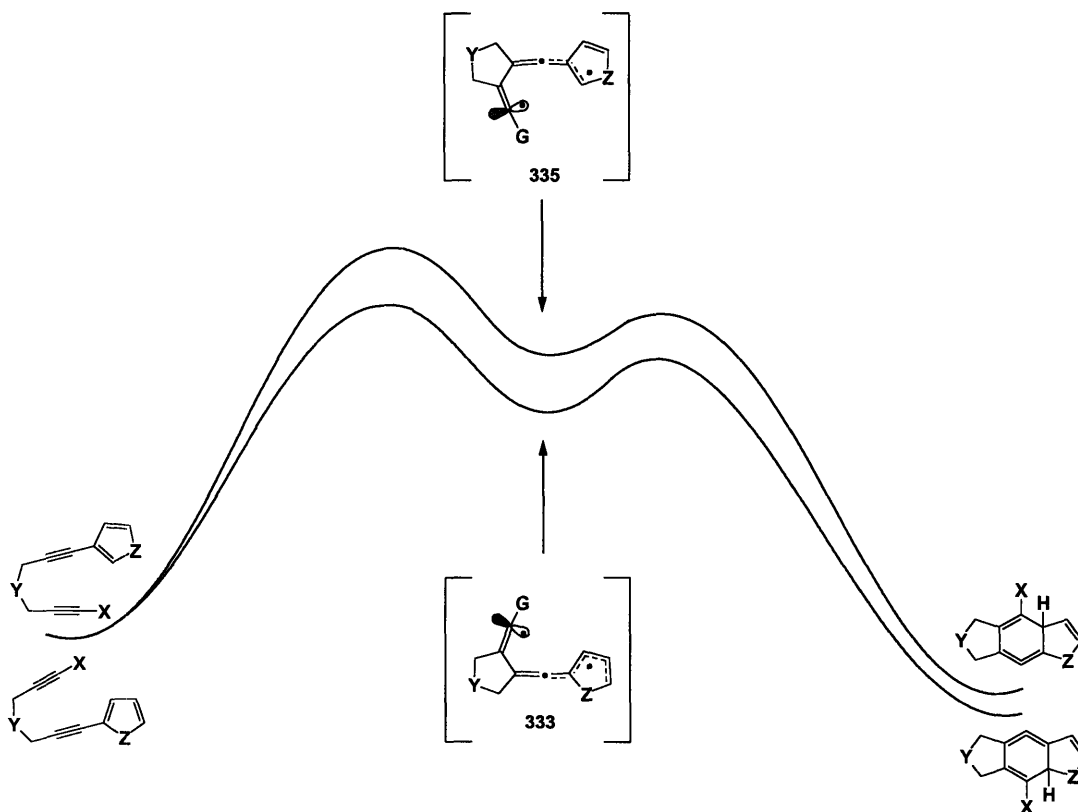
spin density at the indicated carbon when compared to the analogous radical having a phenyl ring at the same position, (i.e., ΔD is positive). This implies that the 2-hetaryl radicals are more stable than the phenyl analog. Note that the 3-hetaryl radicals **336c** and **336d** analogs have a negative ΔD , meaning they display a lower degree of delocalization relative to the phenyl analog, and thus even less than the 2-hetaryl analogs. Therefore, according to this study, 2-hetaryl-substituted radicals are more stable than 2-hetaryl-substituted radicals.

	$\Delta D = D_{Ph} - D_{Ar}$
 <p>334c</p>	+0.61
 <p>334d</p>	+0.49
 <p>336c</p>	-0.12
 <p>336d</p>	-0.33

An older study of the relative rates of methanolysis of 2- and 3-chloromethylfurans and -thiophenes revealed that the activation energies for the solvolysis of the 3-chloromethylhetarenes are about 2-3 fold higher than for the solvolysis of 2-chloromethylhetarenes.¹⁴¹ One could extrapolate all this data, as well as the known reactivity trend for electrophilic aromatic substitution for five-membered

¹⁴¹ Galbershtam, M. A.; Prokofeva, A. F. *Khimiya i Khimicheskaya Tekhnologiya* **1964**, 7, 598.

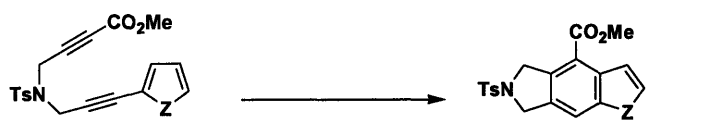
hetarenes, which favors substitution at C-2 over C-3 due to better stabilization of the σ -complex, to estimate that biradical **333** should be more stable than **335**. According to the calculations by Ananikov discussed above, the formation of these biradicals is an endothermic process, and thus any factors that stabilize biradicals **333** and **335** will also stabilize the transition state leading to their formation. Again, if the relative energy of substrates **1** and **216** was similar, it would be expected that the activation barrier for the formation of **333** should be lower than for **335**, leading to a faster reaction; however, if as discussed above the difference in energy between **1** and **216** were to be significant, then a cycloaddition of these substrates via a concerted pathway could proceed at different rates. Perhaps calculations like the ones performed by Ananikov and Saá will provide more insight into these differences between 2- and 3-tethered hetarenyne cycloaddition substrates and clarify these differences quantitatively.



2.2.4. Heteroatom within the Hetarene

The trend of reactivity observed for similar cycloaddition substrates bearing different hetarenes is pyrrole \geq furan $>$ thiophene, as summarized in Tables 9 and 10 (see section 2.5 for quantitative kinetic studies on hetarenyne cycloadditions).


Table 9. Comparison of Cycloadditions of an Alkynyl Pyrrole and an Alkynyl Thiophene



substrate	Z	conditions	cycloadduct	isolated yield (%)
243	NBoc	3 equiv BHT benzene reflux, 15 h*	307	57
271	S	3 equiv BHT toluene reflux, 6 h	316	70

*when performed in refluxing toluene this reaction was complete within 1 h

Table 10. Comparison of Cycloadditions of an Alkynyl Pyrrole and an Alkynyl Furan



substrate	Z	conditions	cycloadduct	isolated yield (%)
232	NBoc	3 equiv BHT benzene reflux, 2 h	310	48
277	O	3 equiv BHT benzene reflux, 4 h	337	74

The degree of aromaticity of monohetarenes follows the trend of thiophene $>$ pyrrole $>$ furan,¹⁴² so if one assumes that the facility of the cycloaddition reaction parallels the ease of disruption of the aromaticity of the hetarene in the transition state, one would expect the relative reactivity to be furan \sim *N*-Boc-pyrrole $>$ thiophene.

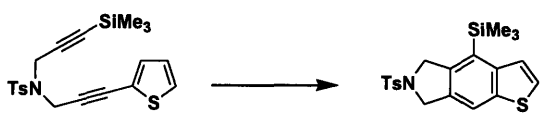
¹⁴² For a review, see reference 1c and Simkin, V. I.; Minkin, V. I.; Glukhovtsev, M. N. *Adv. Heterocycl. Chem.* **1993**, 56, 303.

However, the lower electronegativity of nitrogen makes pyrrole more electron rich than furan, which may impart a higher reactivity to alkynyl pyrroles as 4π components in these cycloaddition reactions. The data available from intermolecular Diels-Alder cycloadditions of vinylpyrroles and vinylfurans does not show a clear difference in reactivity between these two systems (see Section 2.1 of this chapter). Note that all of our experiments with pyrroles involved the protection of the nitrogen on the pyrrole ring with an electron-withdrawing group, which may have skewed the natural trend in reactivity to the one observed in our experiments.

2.3. Effects of Additives and Solvents on Heterenyne Cycloadditions

As already discussed, previous experience in the Danheiser group with enyne cycloadditions revealed that addition of phenolic compounds to cycloaddition reaction mixtures generally results in a 10-20% increase in the yield of product. The same effect was seen with heterenyne cycloadditions as illustrated in Table 11 below.

Table 11. Cycloaddition of an Alkynyl Thiophene in the Presence and Absence of BHT



	270	→	315
		conditions	isolated yield (%)
		3 equiv BHT toluene 160 °C, 16 h	75
		toluene 150 °C, 16 h	53

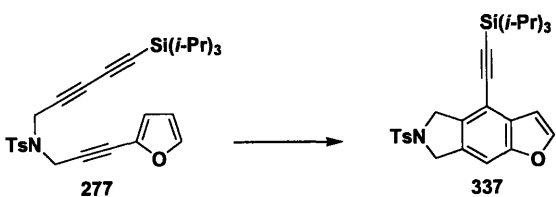
As previously discussed, the beneficial effect of phenolic additives are likely due to their inhibition of polymerization of the starting material as well as their ability to facilitate the isomerization of the cyclic allene intermediate to the aromatic product via

either protonation or hydrogen atom donation to the central carbon of the allene. As discussed in more detail in Section 2.5, these additives have been shown to have no effect on the rate, as expected if they intervene subsequent to the rate-determining cycloaddition step.

The only furan substrate successfully prepared for our cycloaddition studies (**277**) was used to further investigate the effect of phenolic additives, as well as the effects of using protic solvents, with the goal of finding alternate conditions that do not involve large amounts of additives like BHT. Previous studies by Martin Hayes had shown that ethanol and trifluoroethanol can be successfully used as co-solvents (with toluene) in enyne cycloadditions.

The ease of the cycloaddition reaction of furan diyne substrate **277** in refluxing benzene led us to explore ethanol as an alternate solvent for this cycloaddition, given the nearly identical boiling point of ethanol and benzene. The result of these investigations is shown in Table 12 below.

Table 12. Cycloaddition of an Alkynyl Furan Under Different Reaction Conditions



conditions	isolated yield (%)
benzene reflux, 4 h	47
3 equiv BHT benzene reflux, 4 h	74
ethanol reflux, 4 h	63-70
3 equiv BHT ethanol reflux, 4 h	69
trifluoroethanol reflux, 4 h	54

As shown in Table 12, it can be seen that addition of BHT to the reaction mixture in benzene increases the yield of the reaction, in this case by 27%. Interestingly, performing the reaction in ethanol as the solvent (without BHT) produced a cleaner reaction and the yield was nearly identical to that observed in benzene in the presence of BHT. Furthermore, ethanol alone is able to facilitate the isomerization of the cyclic allene to the aromatic product, since addition of BHT to the ethanol solution resulted in no further benefit. It was a surprise that using the more acidic solvent trifluoroethanol led to a decrease in the yield of product. This could be due in part to side reactions associated with protonation of the furan under the more acidic conditions, which may then lead to polymerization and/or decomposition.

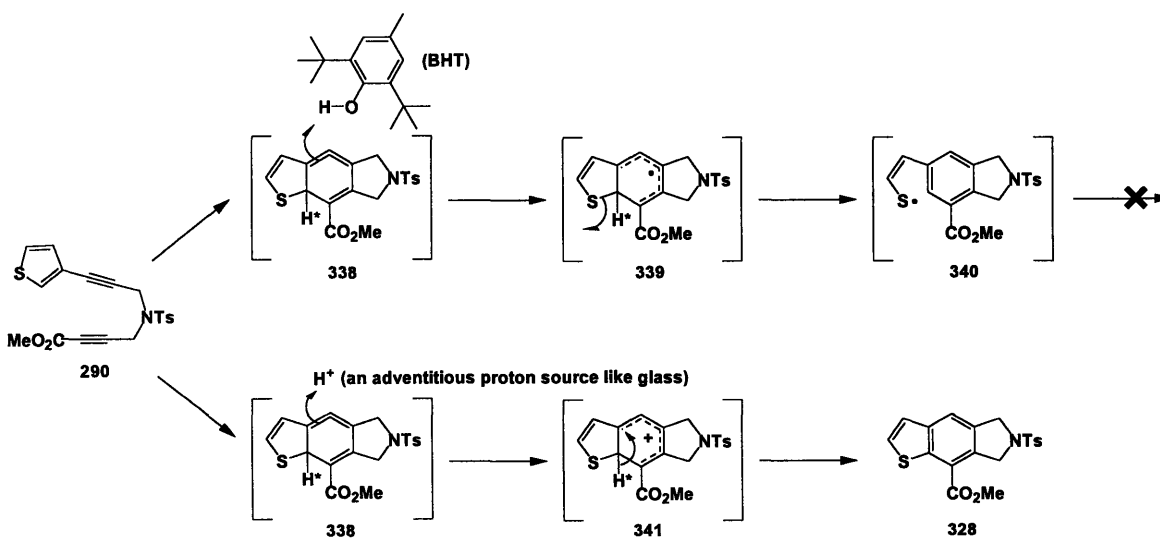
As shown in Table 13 below, ethanol was also effectively used with pyrrole substrate **243**. With this substrate, there seemed to be an increase in the rate of the reaction in ethanol relative to benzene, since the reaction was complete in about half the time. Nevertheless, the yield of the reaction performed in ethanol alone was comparable to that done in benzene with BHT.

Table 13. Cycloaddition of an Alkynyl Furan Under Different Reaction Conditions

conditions	isolated yield (%)
3 equiv BHT benzene reflux, 15 h	57 (R = CO ₂ t-Bu)
ethanol reflux, 8 h	57 (R = CO ₂ t-Bu)
trifluoroethanol reflux, 4 h	63 (R = 1:1 H:CO ₂ t-Bu)

Interestingly, when the cycloaddition of **243** was performed in trifluoroethanol, it was complete in 4 h and a 1:1 mixture of N-Boc and N-H products was obtained in 63% overall yield. In this case, the increased acidity of the solvent may be contributing to the cleavage of the N-Boc protecting group. It is believed that in all three cases the reactions were carefully monitored to ensure the accuracy of the time required for complete consumption of the starting material, so it is unclear why the reactions performed using the alcohols as solvents took less time.

As briefly mentioned in the beginning of Section 2.2.3 of this chapter, it was serendipitously discovered that addition of BHT to the reaction mixture of 3-tethered thiophene substrate **290** led to no formation of desired product due to decomposition of the starting material. The elucidation of what is believed to be the underlying cause of this result was one of the more difficult problems encountered as part of this research, but a reasonable explanation can be provided, in part related to the discussion already presented in Part I, Section 1.5.1 regarding the photocyclization of stilbenoid (bisthienyl)ethenes.



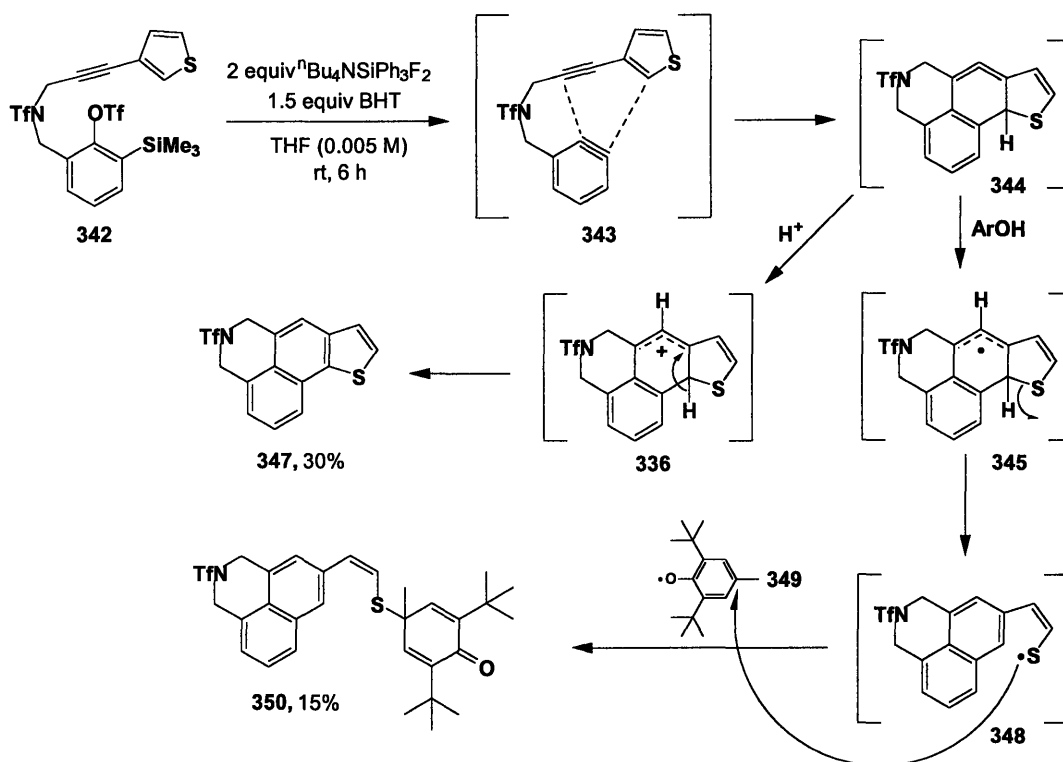
If one considers the cyclic allene intermediate **338** resulting from the cycloaddition of **290**, two possible pathways will determine its ultimate fate. If cyclic

allene **338** abstracts a hydrogen atom from BHT, pentadienyl radical **339** will result, which can then aromatize via two possible routes, either by abstraction of the H^{*}, or via fragmentation of a vinyl thiyl radical to furnish **340**, in a fashion analogous to that reported by Kellogg with (bisthienyl)ethenes (see pp 20-21).¹⁵ Since decomposition of the starting material was the ultimate outcome, it seems that in this particular substrate BHT is acting as a hydrogen atom donor and that the resulting pentadienyl radical **339** then aromatizes via fragmentation to give vinyl thiyl radical **340**. As in Kellogg's report, radical **340** presumably leads to decomposition.

In the absence of BHT, perhaps an adventitious source of acid (e.g., glass) protonates the cyclic allene and the resulting pentadienyl cation **341** can aromatize via loss of a proton, leading to the desired product **328**. Since these reactions are run under conditions of high dilution, in the absence of any additive a given cyclic allene molecule is more likely to react via undesired side reactions leading to decomposition and/or polymerization. This could explain the low yield of 45% under these conditions.

A serendipitous discovery by Martin Hayes provided strong evidence for the formation of the proposed vinyl thiyl radical. Hayes was studying the use of arynes as 2π components in enyne cycloadditions and upon learning of the good reactivity of hetarenynes in [4+2] cycloadditions he decided to construct some of his substrates with this functionality as the 4π component. When Hayes subjected substrate **342** to the typical reaction conditions involving TBAT and BHT in THF under high dilution, a mixture of two products was obtained consisting of the desired product **347** (30% yield) and a second product **350** in 15% yield. The unusual by-product **350** seems to have resulted from the trapping of vinylthiyl radical **348** by the radical of BHT (**349**). This result strengthens the notion that BHT acts differently with different substrates, in some

cases being more of a hydrogen atom donor than a proton source, and in other cases doing the opposite.



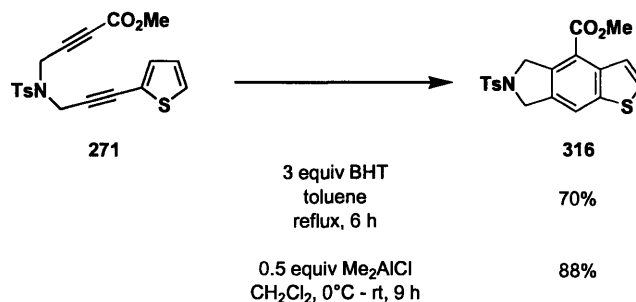
This is evidenced with the cycloaddition of 342, which successfully underwent cycloaddition unlike hetarenyne substrate 290. Thus, the major product 347 could be the result of protonation of cyclic allene 344 by BHT, although hydrogen atom abstraction from 345 is also possible. Minor product 350 could only result from hydrogen atom abstraction from BHT, followed by fragmentation and trapping. In contrast with 339, perhaps some special feature in vinylthiyl radical 345 endows it with additional stabilization and makes it sufficiently long-lived as to be trapped by BHT before reacting via other pathways.

2.4. Thermal versus Lewis Acid-Promoted Hetarynyne Cycloadditions

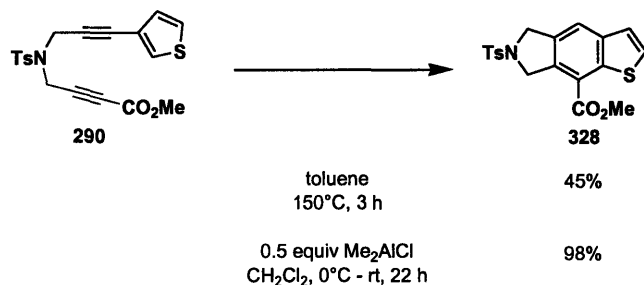
The use of Lewis acids to facilitate chemical reactions is a well known and widely used process.¹⁴³ The Diels-Alder reaction is one of the transformations in which Lewis acid catalysis has been greatly exploited.⁶⁹ Previous work in the Danheiser group on enyne cycloadditions demonstrated the applicability of Lewis acids as promoters in this chemistry, in particular with substrates bearing Lewis-basic functionalities like carbonyl groups.

Consequently, we undertook an investigation of the possibility of promoting hetarenyne cycloadditions using Lewis acids with the hope of developing mild conditions for effecting these reactions. Whether this class of cycloadditions would be amenable to promotion with Lewis acids was not clear at the outset of this work. Previous work on arenene cycloadditions had indicated that those reactions are not subject to promotion with Lewis acids,^{64b} a finding consistent with a stepwise mechanism for the ring-forming step (as compared to concerted cycloaddition in the case of enynes).

Reacting hetarenyne substrates having methyl esters attached to the 2π component with certain Lewis acids indeed has a dramatic enhancing effect on the facility of the reaction, also resulting in a significant improvement in the yield.

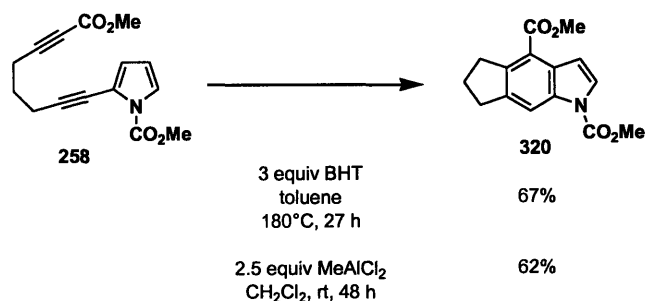


¹⁴³ For a general review of Lewis acids and their applications, see: Corma, A.; García, H. *Chem. Rev.* **2003**, *103*, 4307.



Use of sub-stoichiometric amounts of Me₂AlCl reduced the temperature required for thiophene **271** to undergo cycloaddition from 110 °C to rt, with an 18% increase in the yield of cycloadduct **316**. Similarly, treatment of the 3-tethered analog **290** under similar conditions yielded the desired cycloadduct in nearly quantitative yield after 22 h at rt, in contrast to the reaction in the absence of the Lewis acid which required heating to 150 °C. It is believed that the much lower temperature required for the cycloadditions of **271** and **290** in the presence of Lewis acids reduces the side reactions that at elevated temperatures lead to decomposition. Note that in the case of **290** it had been found necessary to carry out the thermal cycloaddition in the absence of BHT (see page 91 and the discussion on pp 102-104).

In the case of pyrrole substrate **258** with an “all-carbon” tether, a more reactive Lewis acid was necessary due to the low reactivity of the substrate, as can be seen by the relatively high temperature required for the thermal cycloaddition.

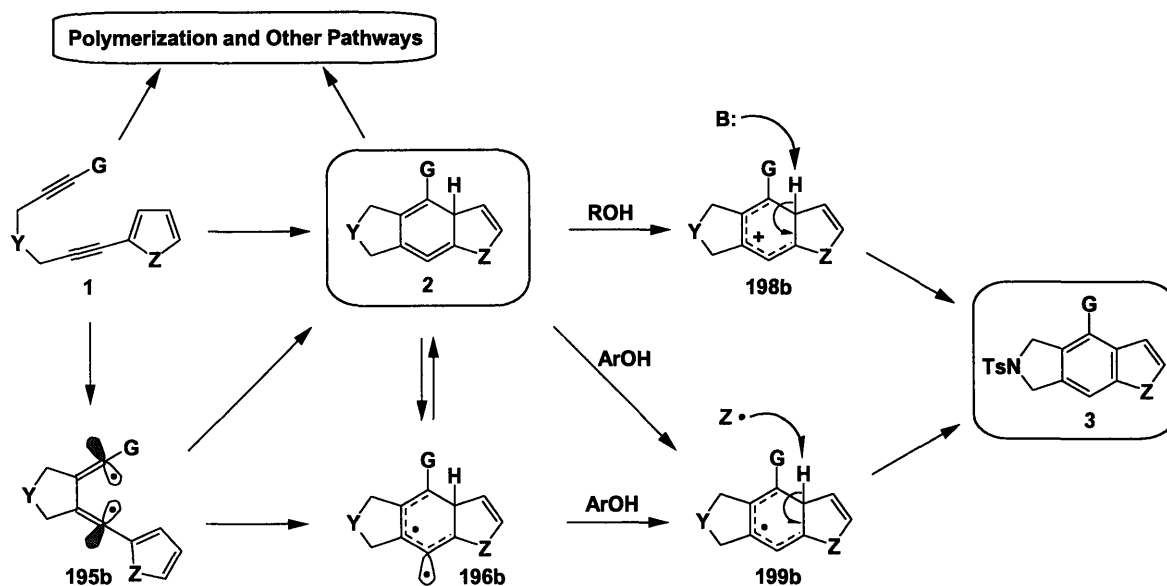


Initially our attempts to accomplish cycloadditions with *N*-*t*-butoxycarbonyl-protected pyrroles using Lewis acids led to decomposition of the starting materials. It is well known that Lewis acids can be used to cleave Boc protecting groups,¹⁴⁴ so *N*-carbomethoxy was next examined as an alternative for protecting the pyrrole in these Lewis acid experiments. Sub-stoichiometric amounts of Lewis acid led to little or no reaction, and only an excess of two or more equivalents led to observable reaction. This could be due to various effects which are not mutually exclusive: (1) the possible need for the in situ formation of a more reactive Lewis acid species resulting from complexation of unbound Lewis acid to substrate-bound Lewis acid followed by ionization, yielding a more reactive catalyst that may actually be the one facilitating the observed reaction; (2) the possible sequestration of the Lewis acid present in the reaction mixture by the *N*-carbomethoxy group, which may augment the electron-withdrawing effect of the protecting group on the ring, and (3) the possible sequestration of the Lewis acid present in the reaction mixture by the product of the reaction, which is expected to be more Lewis basic than the substrate by virtue of being attached to an sp² carbon rather than the more electronegative sp alkynyl carbon. Addition of 2.5 equivalents of MeAlCl₂ to pyrrole substrate **258** gave the desired product at rt in about 48 h with a yield that is comparable to the one obtained under thermal conditions. It is not clear why the improvement in yield seen with the thiophenes was not seen with the pyrrole substrate, but perhaps the extended reaction time in the presence of a stronger Lewis acid leads to partial decomposition of the starting material.

¹⁴⁴ (a) Theodoridis, G. *Tetrahedron* **2000**, *56*, 2339. (b) Bosc, D. S.; Lakshminarayana, V. *Synthesis* **1999**, 66. (c) James, K. D.; Ellington, A. D. *Tetrahedron Lett.* **1998**, *39*, 175.

2.5. Kinetic Studies of Hetarenyne Cycloadditions

In order to quantify the observed differences in the rate of cycloaddition between the different substrates described in the previous sections of this chapter, NMR experiments were performed to establish a rate comparison based on the structural features of the substrates. Unfortunately, rigorous kinetic analysis of these reactions is complicated by the multiple processes that take place under the conditions of the cycloaddition. As summarized in the following scheme, the rate of disappearance of the hetarenyne starting material is due to not only [4+2] cycloaddition (presumably the rate-determining step), but also to a variety of other competing decomposition pathways. Consequently, the rate of disappearance of starting material is expected to be considerably faster than the rate of appearance of the ultimate aromatic product.



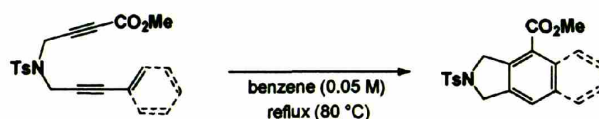
However, interpretation of the kinetic data for the appearance of aromatic product is also difficult, since multiple reaction pathways are available for the presumed intermediate cyclic allene 2 besides the isomerization that leads to product. Although these complications certainly compromise any rigorous quantitative comparison of rates for different cases of the cycloaddition, we nevertheless believed that a preliminary

kinetic study was worthwhile in order to determine whether it might reveal any significant general trends in reactivity with regard to different 2π and 4π components.

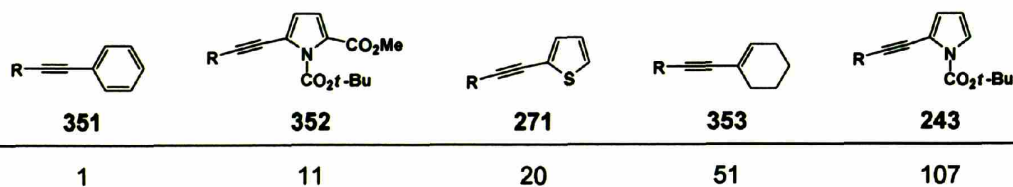
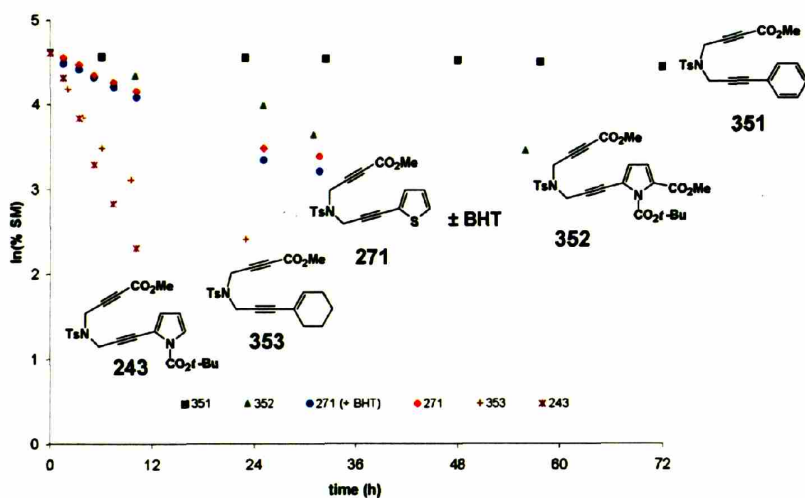
Kinetics experiments were conducted by dissolving cycloaddition substrates in benzene- d^6 at a concentration of 0.05 M and a small amount of anisole was added as an internal standard. The reaction mixtures were heated to reflux and small aliquots were withdrawn at various intervals and dissolved in $CDCl_3$ for NMR analysis. At zero time, the amount of starting material was normalized and this gave a reading for the relative amount of internal standard present. With the assumption that the amount of internal standard did not change, for every subsequent time value the amount of remaining starting material and product formed was measured relative to the value established for the internal standard at zero time, and this was done for at least three time intervals for each substrate in order to obtain enough data for graphical analysis and quantification of relative rates. Two series of data were collected: (1) for substrates bearing the same 2π component (alkynyl ester) attached to various 4π components, and (2) for substrates bearing the same alkynyl pyrrole 4π component but bearing different 2π components. The following discussion is based on the assumption of first order kinetics and that the rate of decomposition of the different substrates by alternative pathways is occurring at a similar rate.

Below is the data for substrates bearing the same 2π component (alkynyl ester) attached to various 4π components. When analyzing the disappearance of the starting material in this series of substrates, the data revealed several interesting trends. First, it is clear that the alkynyl pyrrole **243** reacts faster than all other substrates, about twice as fast as the non-aromatic alkynyl cyclohexene **353**, and more than five times faster than the thiophene substrate **271**. Substrate **352**, which bears an EWG on the pyrrole ring, is consumed at a 10-fold slower rate than **243**, and the substrate that reacts the slowest is

the arenynes **351**. This trend is what would be expected from the combination of electronic factors associated with the presence of a heteroatom within the ring and loss of aromaticity in the transition state. The fact that almost no reaction of **351** occurs under these conditions would seem to suggest that polymerization (or other side reactions involving the α,β -alkynyl ester moiety is not contributing significantly to the disappearance of starting material in the case of the other substrates. However, this question is difficult to evaluate, since once cycloaddition begins to occur, radical species would be generated that could initiate polymerization.

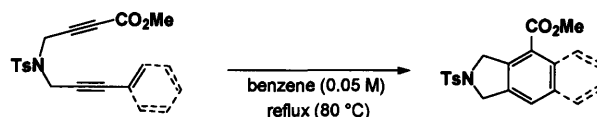


Disappearance of Starting Material – Alkynyl Esters with Different 4 π Components

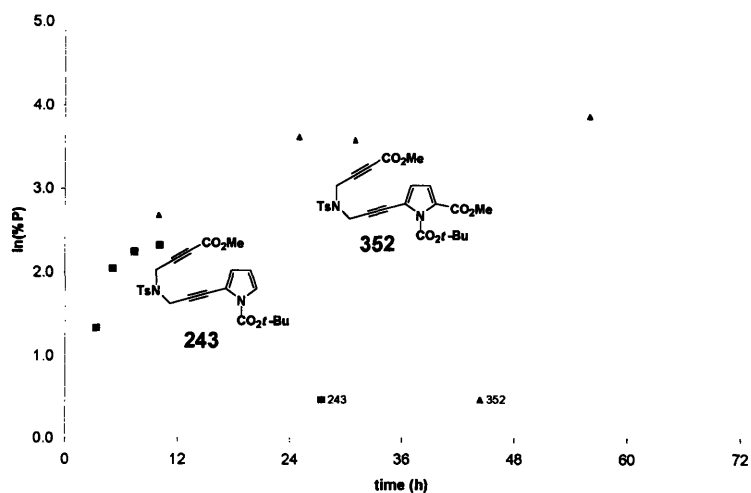


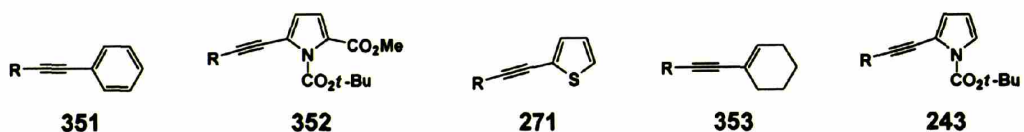
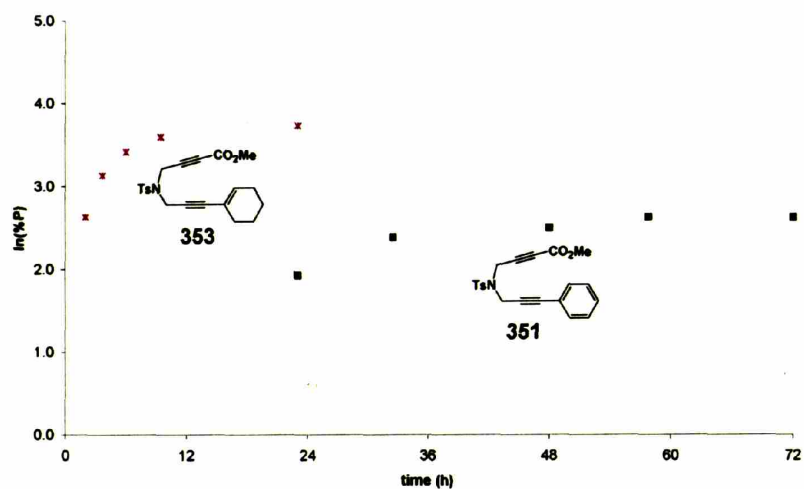
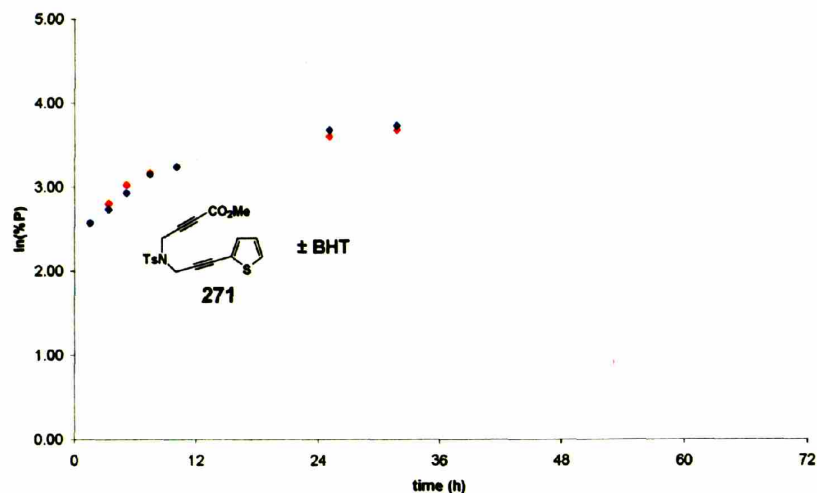
The analysis of the data for appearance of products is complicated by several factors, including the fact that these experiments were conducted in the *absence of BHT* in contrast to the runs discussed in the previous chapter. One exception is the case of the

alkynylthiophene **271**, where the reaction was carried out both in the presence and absence of 3 equiv of BHT. As indicated in these plots, the relative rate of both disappearance of starting material and appearance of product were nearly the same in each case. On the other hand, we believe that the data for the appearance of product is significantly affected by the absence of BHT in the case of other substrates. For example, in the case of the alkynyl pyrrole **243**, only ca. 10% of product was formed after 10 h, although less than 10% of the starting material remained at this time. This contrasts with the preparative scale reaction run in the presence of BHT (see Table 1, page 80) where the cycloadduct was obtained in 57% yield after 15 h. At least in the case of cycloaddition substrates **243**, **352**, and **353**, it appears that in the absence of BHT the intermediate cyclic allene is decomposing by a variety of other pathways in addition to its isomerization to the aromatic product. Consequently, analysis of the relative rates of these reactions based on appearance of aromatic product does not provide meaningful information concerning the rate of [4+2] cycloaddition.



Appearance of Product – Alkynyl Esters with Different 4 π Components





k_{rel}

1

1.8

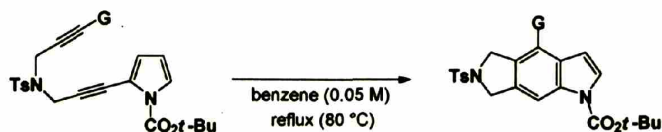
2.6

3.1

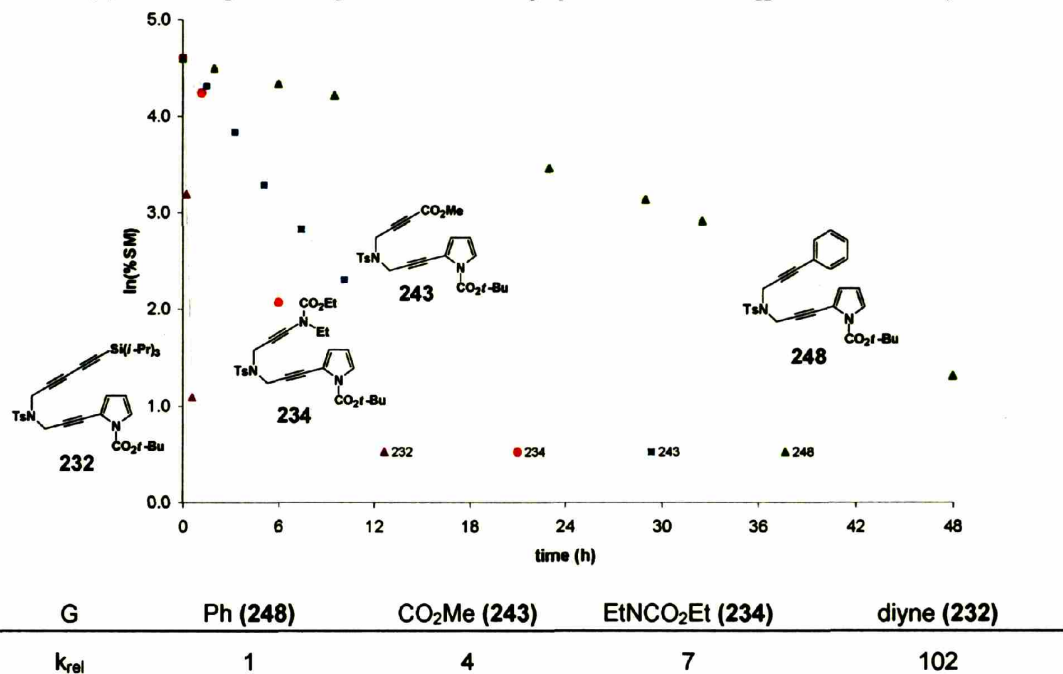
10

In practical terms, these results signify that to efficiently perform these reactions on a preparative scale within a period of 12-24 h, pyrrole substrate **243** would require heating to 80-100°C, whereas phenyl substrate **351** would require temperatures of up to 180-200 °C. The remaining substrates would lie somewhere in between.

Below is the data for the second series of experiments involving the same alkynyl pyrrole 4π component bearing various 2π components.



Disappearance of Starting Material – Alkynyl Esters with Different 2π Components



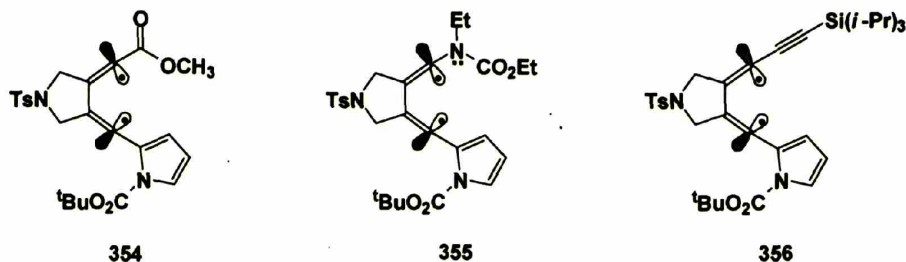
The rate of disappearance of the diyne **232** was found to be about 25 times higher than the alkynyl ester (**243**). Due to the repulsion of the electron-rich π clouds separated by short $C_{sp}-C_{sp}$ bonds, polynes are reactive and unstable species known to polymerize¹⁴⁵ and thus higher energy content in the substrate may contribute to the increase in the reaction rate of diyne **232**. It is important to note that because of the high reactivity of the diyne substrate **232**, there was already product present in the reaction mixture when the experiment with this substrate was begun. Thus, all rate data collected for the disappearance of the starting material for diyne **232** is in the presence of

¹⁴⁵ Jonas, U.; Shah, K.; Norvez, S.; Charych, D. H. *J. Am. Chem. Soc.* **1999**, *121*, 4580.

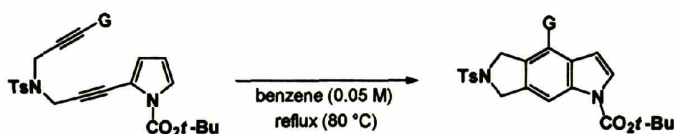
its cycloadduct **310**. Only if cycloadduct **310** were to promote or inhibit the disappearance of the cycloaddition substrate diyne **232** would its presence have an impact on the measured rate of reaction of the diyne **232**, and we believe this is unlikely.

Having a phenyl group as the 2π component, as in **248**, leads to a 25-fold loss in reactivity relative to the carbomethoxy group. An interesting observation was that having a heteroatom directly attached to the 2π component, as in ynamide substrate **234**, seems to have led to a slight enhancement in the rate of reaction relative to the alkynyl ester. This observation that an electron-donating group may serve to accelerate the reaction under these apparent “normal electron demand” conditions could be the result of a difference in energy between the ynamide and alkynyl ester substrates that is translated to the transition states of a concerted reaction. However, it could also be an indication that these reactions may be proceeding via a stepwise pathway if the relative energy of the substrates is comparable and the carbamate is better able to stabilize an adjacent vinyl radical in a stepwise pathway. As previously discussed, a concerted process controlled purely by FMO interactions would show rate retardation with the ynamide and rate enhancement with the ester. However, the similar rate-enhancing effect observed with the ynamide and alkynyl ester could also be explained by the comparable radical-stabilizing ability of nitrogen and carbonyl groups, which can lead to similar stabilities for the radicals **354** and **355** shown below.¹⁴⁶ It is unclear if the higher reaction rate seen with the diyne **232** is due to a similar effect via radical **356** or simply to a relative destabilization of the substrate as described above. As previously suggested, perhaps calculations like the ones performed by Ananikov and Saá will provide more insight into these differences in rate.

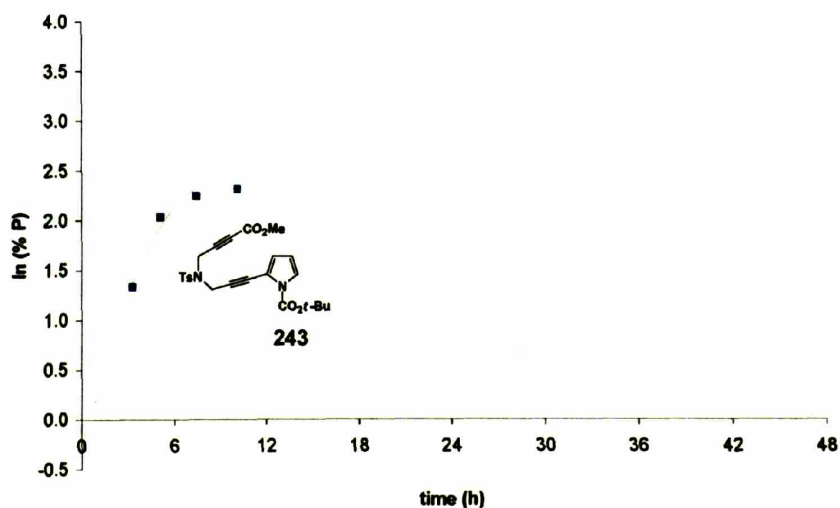
¹⁴⁶ For a discussion of the radical-stabilizing effects of substituents, see reference 65 and: (a) Bordwell, F. G.; Gallagher, T.; Zhangf, X. *J. Am. Chem. Soc.* **1991**, *113*, 3495. (b) *Substituent Effects in Radical Chemistry*; Viehe, H. G., Janousek, Z., Merenyi, R., Eds.; Reidel: Dordrecht, The Netherlands, 1986.

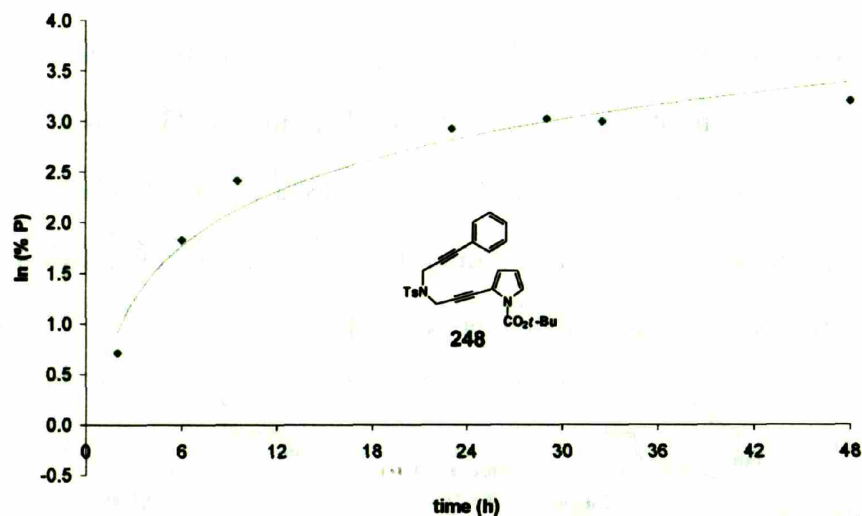
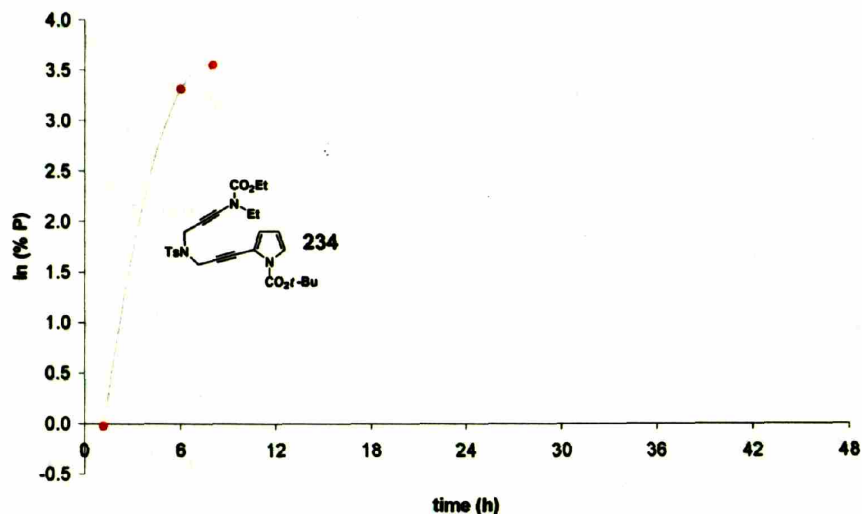


Analyzing the appearance of the product in this second series of cycloaddition substrates again revealed a similar trend. As noted above, when beginning the experiment with diyne **232** the reaction mixture already contained product. Interestingly, the cycloadduct of diyne **232** seems to be unstable, since the amount of cycloadduct decreased with time as the starting material continued to disappear, so the determination of the rate of appearance of the cycloadduct of **232** was not possible. This could explain, at least in part, the low yield of 48% obtained when performing this reaction on a preparative scale, even though this yield is not much lower than the one obtained with the cycloaddition of alkynyl ester **243**.



Appearance of Product – Alkynyl Esters with Different 2π Components



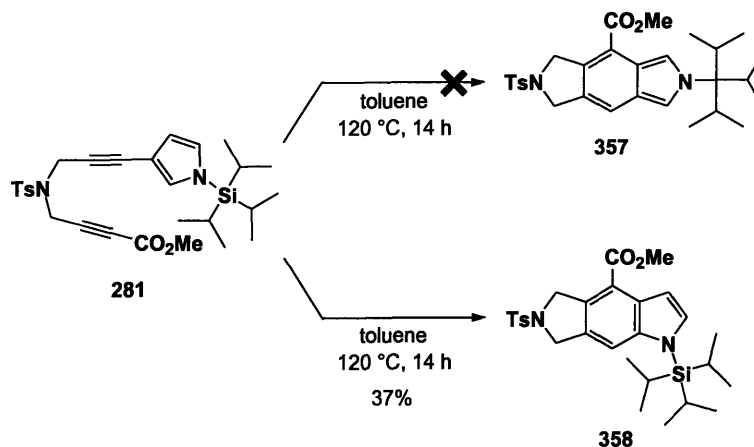


G	Ph (248)	CO ₂ Me (243)	EtNCO ₂ Et (234)	CCSi(<i>i</i> -Pr) ₃ (232)
k_{rel}	1	3	12	cannot be determined

2.6. Miscellaneous Reactions

When first exploring the 3-tethered substrates, the possibility of forming the benzo[*c*]-fused products was considered. However, these products were never identified in any of the systems studied. In an attempt to drive the cycloaddition toward this potential side reaction by way of steric hindrance, cycloaddition of the 3-tethered *N*-TIPS pyrrole substrate 281 was performed, but not even the presence of a very bulky

triisopropylsilyl group was able to drive the cycloaddition toward the formation of isoindole **357**. Instead, indole **358** was obtained in 37% yield.



Concluding Remarks

This dissertation has presented the work undertaken over the last few years to investigate the potential applicability of hetarenyne cycloadditions in organic synthesis as a new and efficient method for the preparation of benzo[b]-fused five-membered heteroaromatic compounds. The research described herein has explored and expanded the scope of hetarenyne cycloadditions and has laid the groundwork for further exploration of the potential this chemistry has as a useful application in the synthesis of more complex molecules.

Part III:
Experimental Section

General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated.

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane, tetrahydrofuran, and diethyl ether were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Pyridine, piperidine, and triethylamine were distilled under argon from calcium hydride. Chlorotrimethylsilane and chlorotriisopropylsilane were distilled under argon from phosphorous pentoxide. Methyl chloroformate was distilled under argon. Acetaldehyde was distilled from CaSO₄. Acetic anhydride was distilled from quinoline. Copper(I) iodide was extracted with THF for 24 h in a Soxhlet extractor and then dried under vacuum (0.1 mmHg). Palladium(II) chloride (bis)triphenylphosphine was recrystallized from boiling chloroform. *n*-Butyllithium was titrated according to the Watson-Eastham method using menthol or BHT in THF at 0 °C with 1,10-phenanthroline as an indicator¹

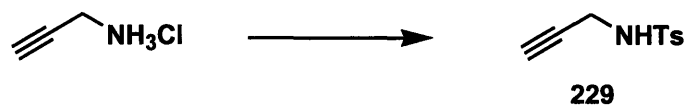
Chromatography

Column chromatography was performed on Silicycle silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Visualization was effected by one or more of the following techniques: (a) ultraviolet irradiation, (b) immersion of the plate in an

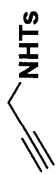
¹ (a) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165. (b) Ellison, R. A.; Griffin, R.; Kotsonis, F. N. *J. Organomet. Chem.* **1972**, *36*, 209.

ethanolic solution of 3% *p*-anisaldehyde containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C, (c) immersion of the plate an ethanolic solution of 3% *p*-vanillin containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C, (d) immersion of the plate in a 10% solution of phosphomolybdic acid in methanol followed by heating to ca. 200 °C, (e) immersion of the plate an aqueous solution of 6% ammonium molybdate and 1% cerium(IV) sulfate containing 12% concentrated sulfuric acid followed by heating to ca. 200 °C, (f) immersion of the plate an aqueous solution of 5% sodium hydroxide containing 1% potassium permanganate and 6% potassium carbonate followed by heating to ca. 200 °C.

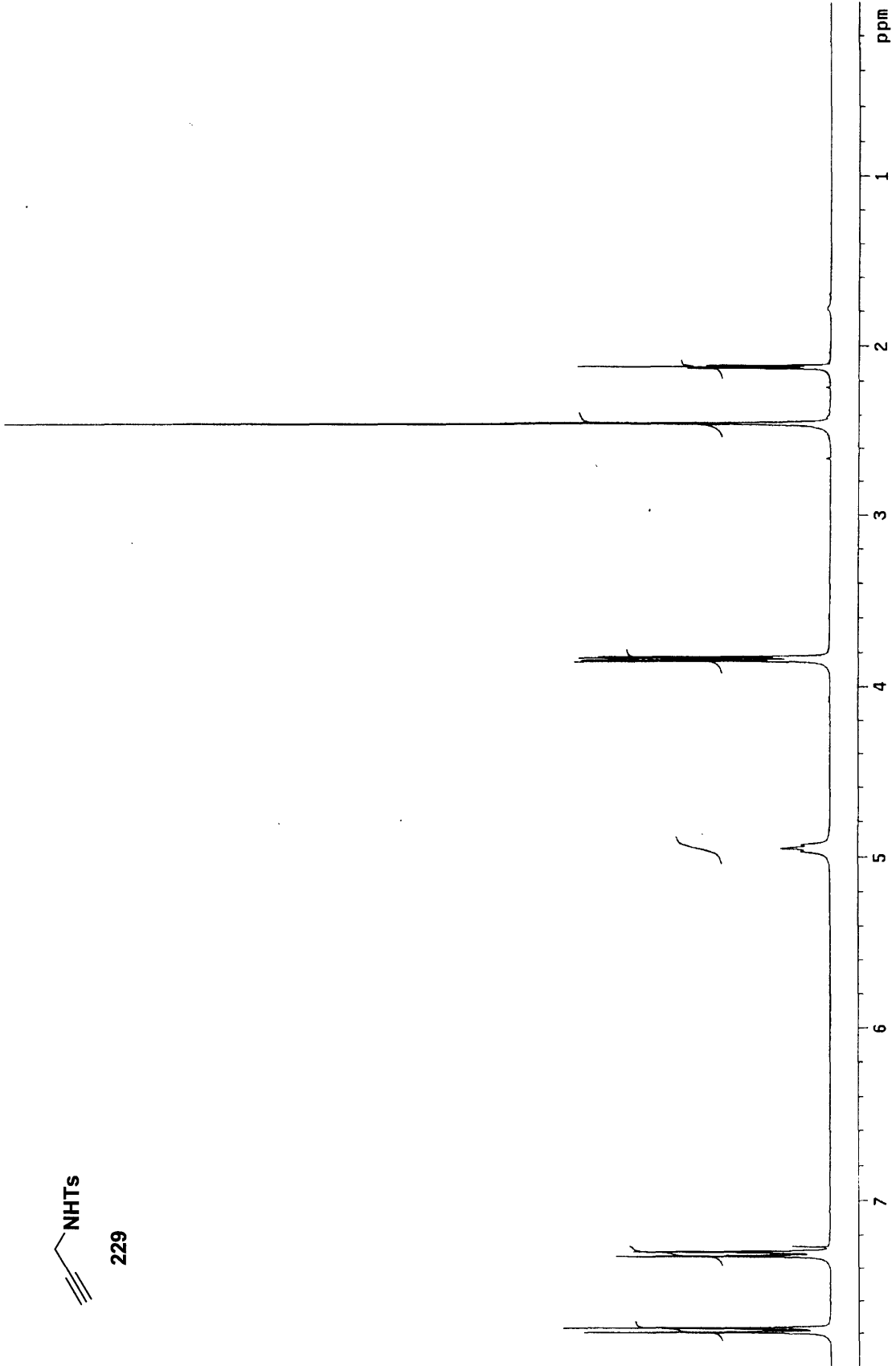
Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on Varian XL-300 (300 MHz), Varian Unity 300 (300 MHz), and Varian Inova 500 (500 MHz) spectrometers. ¹H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the CHCl₃ peak at 7.27 ppm used as a standard). ¹³C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of CHCl₃ at 77.23 ppm used as a standard). Low resolution mass spectra (GC-MS) were measured on a Agilent 6890N series gas chromatograph with Agilent 5973 series mass selective detection. High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 Tesla Fourier transform mass spectrometer.

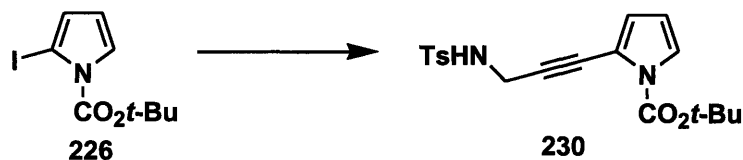


[(4-Methylphenyl)sulfonyl]prop-2-ynylamine (229). A 100-mL, three-necked, round-bottomed flask fitted with a glass stopper, rubber septum, and an argon inlet adapter was charged with 30 mL of CH_2Cl_2 and cooled to 0 °C. Pyridine (6.3 mL, 6.2 g, 78 mmol) and propargylamine hydrochloride (95%, 1.425 g, 15.56 mmol) were then added, and the reaction mixture was stirred at 0 °C until the salt was suspended, followed by the addition of TsCl (3.561, 18.68 mmol) in one portion. The resulting mixture was stirred at rt for 21 h and then diluted with 25 mL of 5% HCl solution and 10 mL of CH_2Cl_2 . The organic phase was separated and washed with two 25 mL of 5% HCl solution, and the combined aqueous phases were extracted with three 50-mL portions of CH_2Cl_2 . The combined organic phases were then dried over MgSO_4 , filtered, and concentrated to give 3.469 g of off-white solid that was dissolved in CH_2Cl_2 and concentrated onto 5 g of silica gel which was added to the top of a column of 50 g of silica gel. Gradient elution with 10-25% EtOAc-hexanes furnished 3.201 g (98%) of sulfonamide **229** as an off-white solid: mp 73-75 °C. Spectral data is consistent with that previously reported (Oppolzer, W.; Ruiz-Montes, J. *Helv. Chim. Acta* **1993**, 76, 1266; Masquelin, T; Obrecht, D. *Synthesis* **1995**, 3, 276).

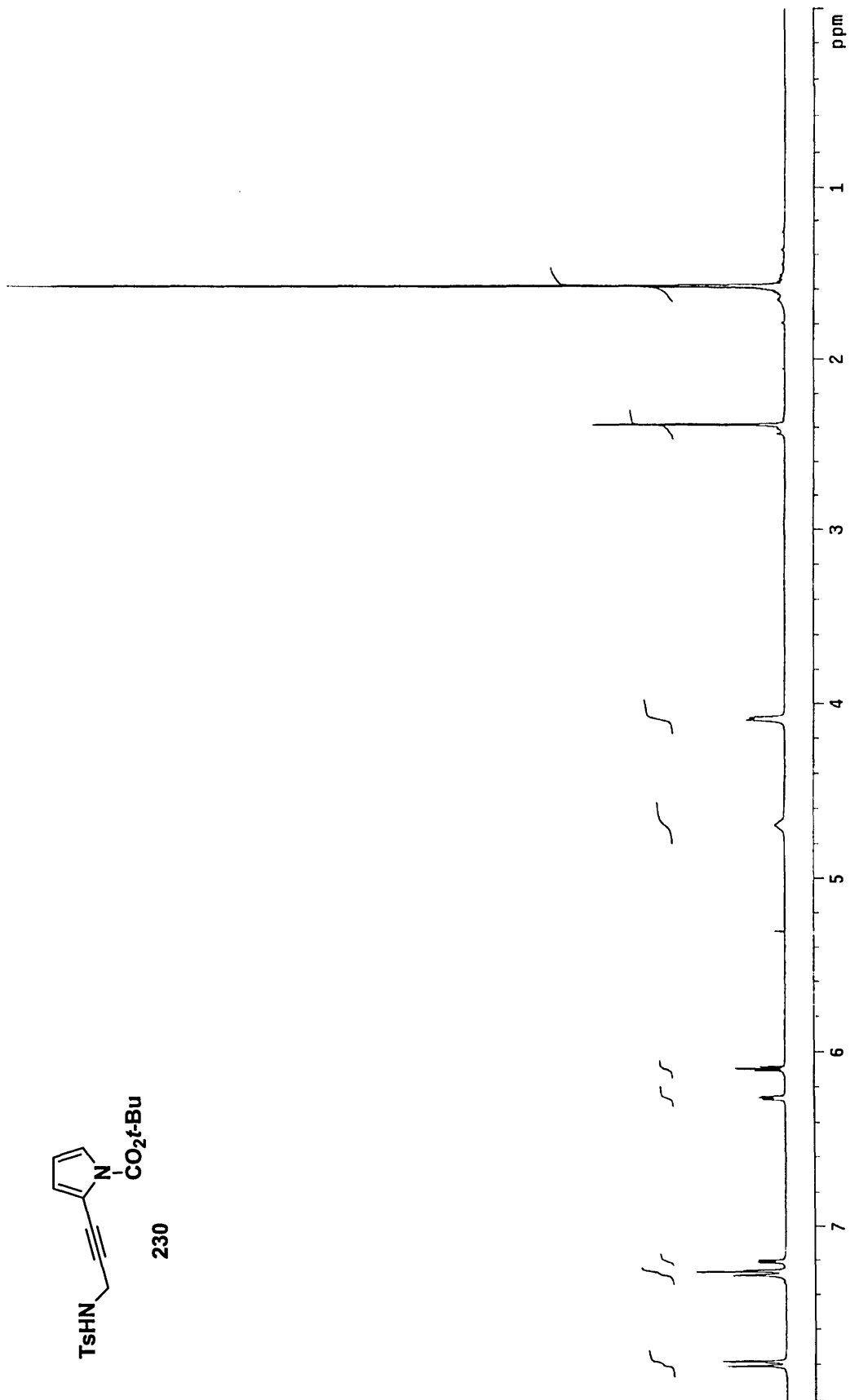
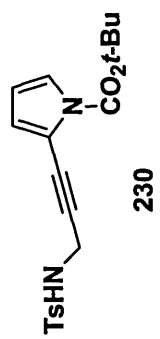


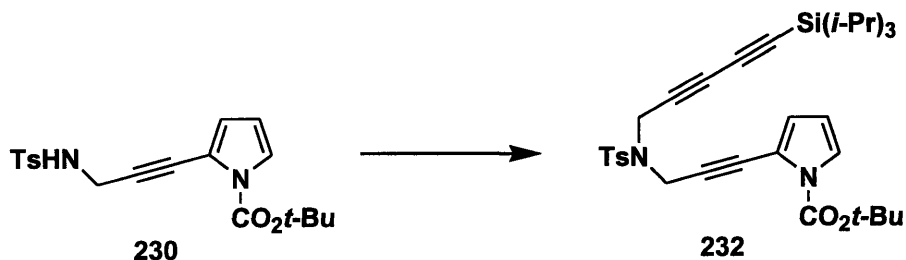
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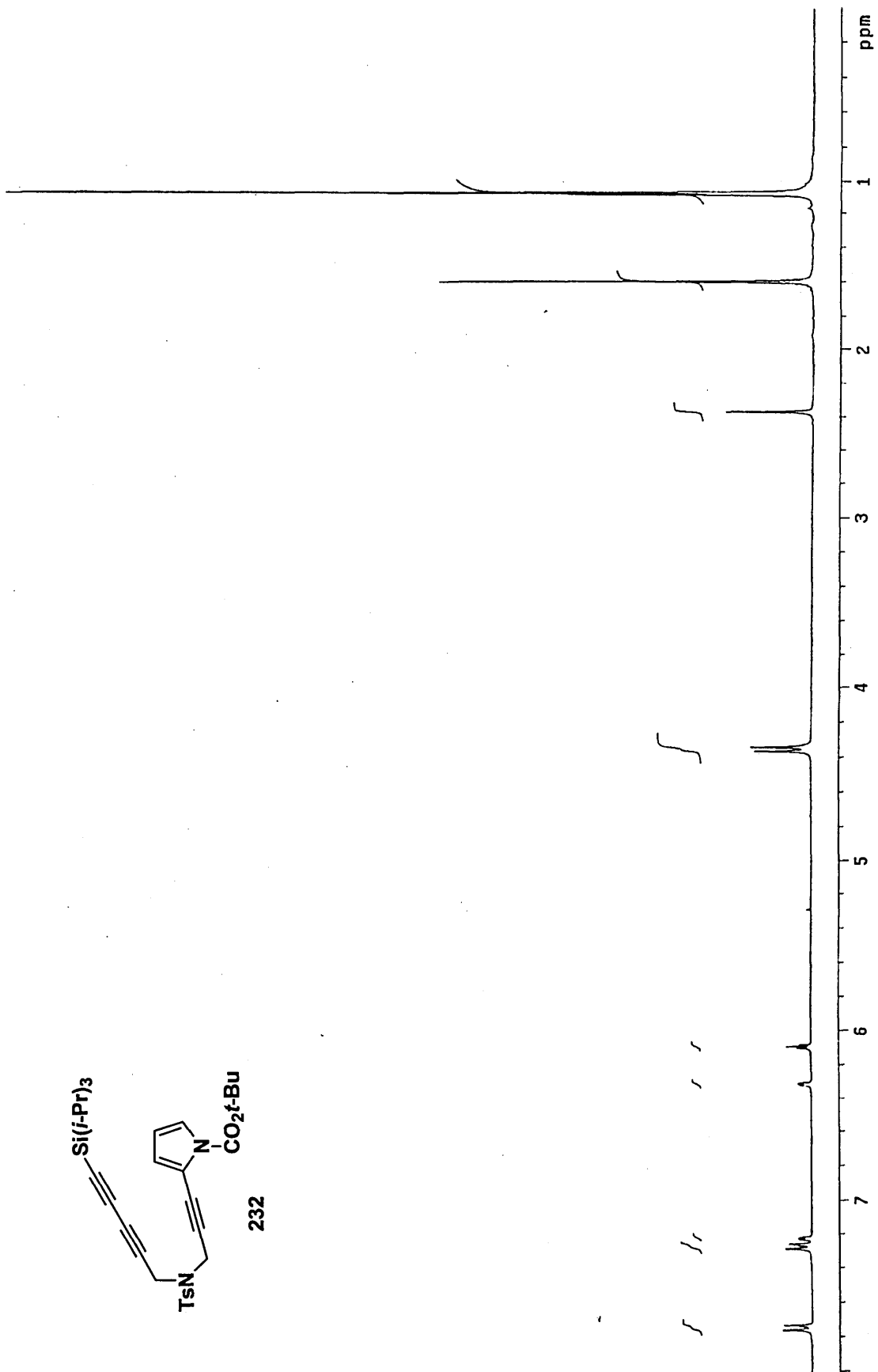
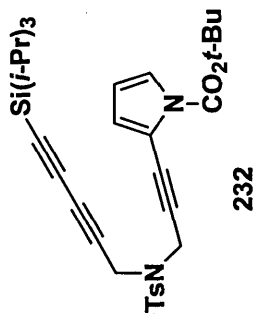


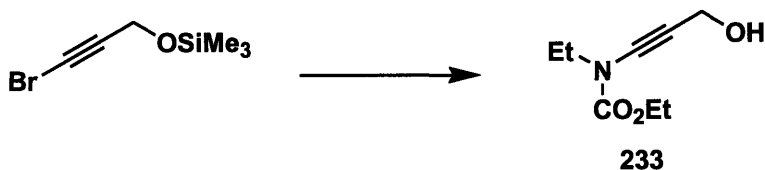
1-(*t*-Butoxycarbonyl)-2-(3-[[4-methylphenyl]sulfonyl]amino}prop-1-ynyl)pyrrole (230). A 50-mL, round-bottomed flask fitted with an argon inlet adapter was charged with the iodopyrrole **226** (1.752 g, 5.977 mmol), 30 mL of THF, and piperidine (3.0 mL, 2.6 g, 30 mmol). Pd(PPh₃)₂Cl₂ (0.216 g, 0.308 mmol), CuI (0.140 g, 0.735 mmol), and sulfonamide **229** (1.377 g, 6.578 mmol) were then added, and the resulting mixture was stirred for 2 h at rt and then filtered through 10 g of silica gel with the aid of 100 mL of diethyl ether. The filtrate was concentrated under reduced pressure to yield 2.974 g of a dark red semisolid that was dissolved in 50 mL of CH₂Cl₂ and concentrated onto 10 g of silica gel which was added to the top of a column of 90 g of silica gel. Gradient elution with 0-25% EtOAc-hexanes afforded 1.960 g (88%) of **230** as a viscous honey-colored oil: IR (thin film) 3283, 2236, 1740, 1598, 1552, and 1319cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, *J* = 8.2 Hz, 2 H), 7.26 (d, *J* = 8.2 Hz, 2 H), 7.20 (dd, *J* = 3.3, 1.6 Hz, 1 H), 6.24 (dd, *J* = 3.6, 1.6 Hz, 1 H), 6.08 (dd, *J* = 3.6, 3.3 Hz, 1 H), 4.93 (s, 1 H), 4.08 (s, 2 H), 2.37 (s, 3 H), and 1.59 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 148.2, 143.8, 136.8, 129.8, 127.6, 122.8, 121.4, 114.3, 111.0, 86.9, 84.6, 77.3, 34.3, 28.1, and 21.7; HRMS (*m/z*): [M+Na⁺] calcd for C₁₉H₂₂N₂O₄S 397.1192; found, 397.1205.



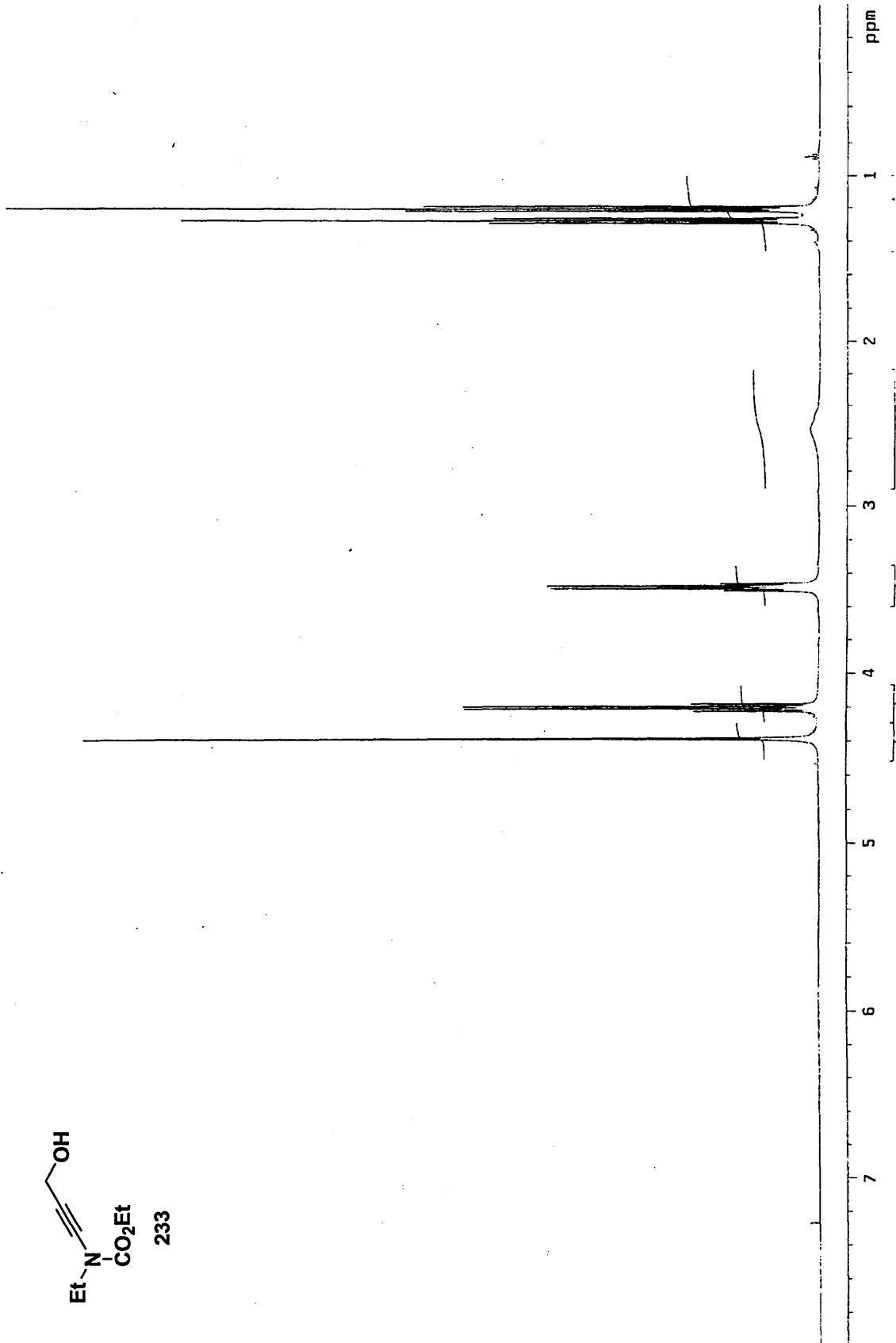
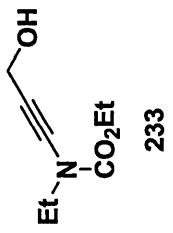


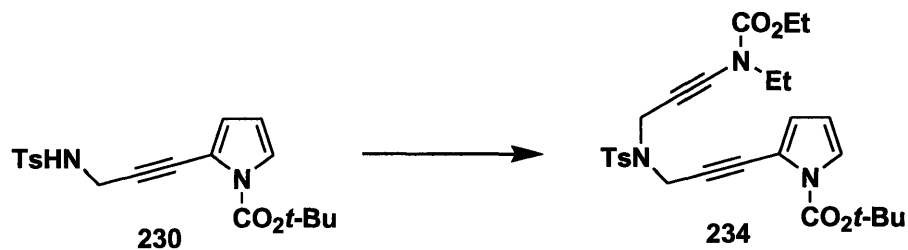
1-(*t*-Butoxycarbonyl)-2-(3-{[(4-methylphenyl)sulfonyl]-5-(triisopropylsilyl)penta-2,4-diynylamino}prop-1-ynyl)pyrrole (232). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with the sulfonamide **230** (0.376 g, 1.00 mmol), 10 mL of THF, triphenylphosphine (0.316 g, 1.20 mmol), and alcohol **231**⁸⁸ (0.274 g, 1.16 mmol). Diisopropyl azodicarboxylate (DIAD) (0.24 mL, 0.25 g, 1.16 mmol) was added dropwise via syringe over 1 min, and the reaction mixture was stirred at rt for 3 h and then concentrated under reduced pressure to furnish 1.276 g of a brown semisolid. This material was dissolved in 50 mL of CH₂Cl₂ and concentrated onto 5 g of silica gel which was added to the top of a column of 45 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes provided 0.343 g (58%) of **232** as a viscous brown oil: IR (thin film) 2233, 2106, 1745, 1598, 1552, and 1319 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 7.23 (dd, *J* = 3.3, 1.7 Hz, 1 H), 6.32 (dd, *J* = 3.4, 1.7 Hz, 1 H), 6.10 (dd, *J* = 3.4, 3.3 Hz, 1 H), 4.37 (s, 2 H), 4.35 (s, 2 H), 2.37 (s, 3 H), 1.60 (s, 9 H), and 1.18-0.97 (m, 21 H); ¹³C NMR (75 MHz, CDCl₃) δ 148.3, 144.1, 135.2, 129.7, 128.2, 122.8, 121.4, 114.3, 111.0, 89.0, 85.1, 84.6, 83.9, 78.7, 71.1, 69.9, 38.1, 37.4, 28.1, 21.7, 18.7, and 11.3; HRMS (*m/z*): [M+Na⁺] calcd for C₃₃H₄₄N₂O₄SSi 615.2683; found, 615.2697.



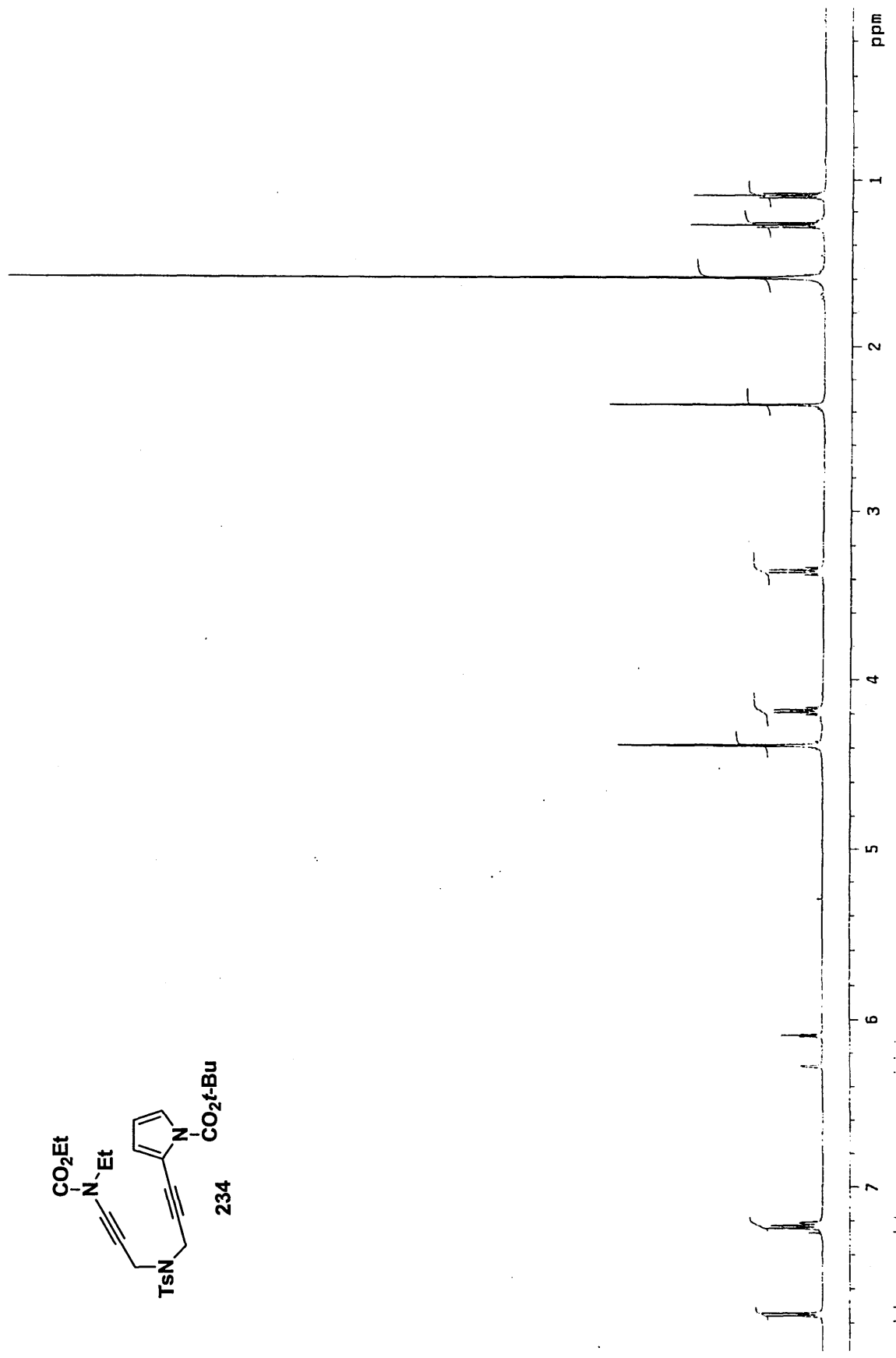
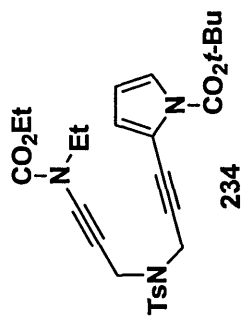


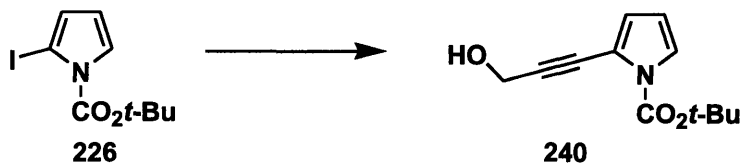
N-Carboethoxy-N-[3-hydroxyprop-1-ynyl]ethylamine (233). A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and addition funnel fitted with a rubber septum and argon inlet needle was charged with a solution of EtNHCO₂Et (0.80 mL, 0.78 g, 6.7 mmol) in 25 mL of pyridine and cooled to 0 °C. KHMDS solution (0.91 M in THF, 7.2 mL, 6.6 mmol) was added via syringe over 2 min, and the resulting mixture was stirred at 0 °C for 10 min. A solution of CuI (1.364 g, 7.162 mmol) in 15 mL of pyridine was transferred into the reaction mixture via cannula over 1 min from a 25-mL pear-shaped flask (10 mL pyridine rinse). The reaction mixture was then stirred at rt for 2 h, and a solution of the bromoalkyne (1.236 g, 5.968 mmol) in 10 mL of benzene was added via the addition funnel (5 mL pyridine rinse) over 20 min. The addition funnel was replaced with a glass stopper, and the reaction mixture was then stirred at rt for 20 h. The resulting mixture was diluted with 100 mL of ether and 100 mL of a 2:1 solution of brine and concd aq NH₄OH soln. The organic phase was separated and washed with two 100-mL portions of the brine-NH₄OH solution, and the combined aqueous phases were extracted with three 100-mL portions of ether. The combined organic phases were then washed with 100 mL of brine, dried over MgSO₄, filtered, and concentrated to give 1.990 g (116% crude yield) of a dark-brown oil that was added to the top of a column of 50 g of silica gel. Elution with hexanes furnished 0.121 g (7%) of a light-brown oil that was dissolved in 1.5 mL of THF in a 5-mL round bottomed flask fitted with a rubber septum and argon inlet needle. To this solution was added 1.5 mL of TBAF solution (1.0 M in THF, 1.5 mmol), and the resulting mixture was stirred at rt for 30 min. The reaction mixture was diluted with 10 mL of ether and 10 mL of water, and the aqueous phase was separated and extracted with four 10-mL portions of ether. The combined organic phases were dried over MgSO₄, filtered, and concentrated to give 0.104 g of a light-brown paste that was concentrated onto 1 g of silica gel which was added to the top of a column of 10 g of silica gel. Gradient elution with 0-20% EtOAc-hexanes furnished 0.066 g (6%, from the bromoalkyne) of ynamide **233** as a light brown oil : IR (thin film) 3427, 2255, and 1703 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.39 (s, 2 H), 4.20 (q, *J* = 7.2, 2 H), 3.48 (q, *J* = 7.2, 2 H), 2.55 (broad s, 1 H), 1.28 (t, *J* = 7.2, 3 H), and 1.21 (t, *J* = 7.2, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 155.6, 79.2, 69.2, 63.3, 51.2, 45.2, 15.6, and 13.1; HRMS (*m/z*): [M+Na⁺] calcd for C₈H₁₃NO₃ 194.0788; found, 194.0789.



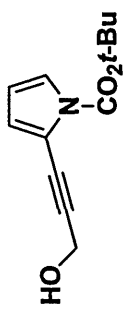


1-(*t*-Butoxycarbonyl) 2-(3-{{3-(ethoxy-*N*-ethylcarbamoyl)prop-2-ynyl}}[(4-methylphenyl)-sulfonyl]amino}prop-1-ynyl)pyrrole (**234**). A 5-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with the sulfonamide **230** (0.131 g, 0.351 mmol), 2 mL of THF, triphenylphosphine (0.102 g, 0.387 mmol), and alcohol **233** (0.063 g, 0.37 mmol). Diisopropyl azodicarboxylate (DIAD) (0.080 mL, 0.082 g, 0.41 mmol) was added dropwise via syringe over 1 min, and the reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure to furnish 0.400 g of a dark-red paste. This material was dissolved in 10 mL of CH₂Cl₂ and concentrated onto 1 g of silica gel which was added to the top of a column of 20 g of silica gel. Gradient elution with 0-10% EtOAc-hexanes provided 0.061 g (33%) of **234** as a viscous brown oil: IR (thin film) 2259, 1726, 1598, 1551, and 1319 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 7.21 (dd, *J* = 3.2, 1.7 Hz, 1 H), 6.32 (dd, *J* = 3.4, 1.7 Hz, 1 H), 6.10 (dd, *J* = 3.4, 3.2 Hz, 1 H), 4.39 (s, 4 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.35 (q, *J* = 7.1 Hz, 2 H), 2.36 (s, 3 H), 1.60 (s, 9 H), 1.28 (t, *J* = 7.1 Hz, 3 H), and 1.10 (t, *J* = 7.1 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 155.3, 148.2, 143.7, 135.8, 129.6, 128.1, 122.7, 121.2, 114.5, 111.0, 85.6, 84.5, 78.0, 63.2, 37.6, 37.3, 28.1, 21.7, and 14.6; HRMS (*m/z*): [M+Na⁺] calcd for C₂₇H₃₃N₃O₆S 550.1988; found, 550.1956.

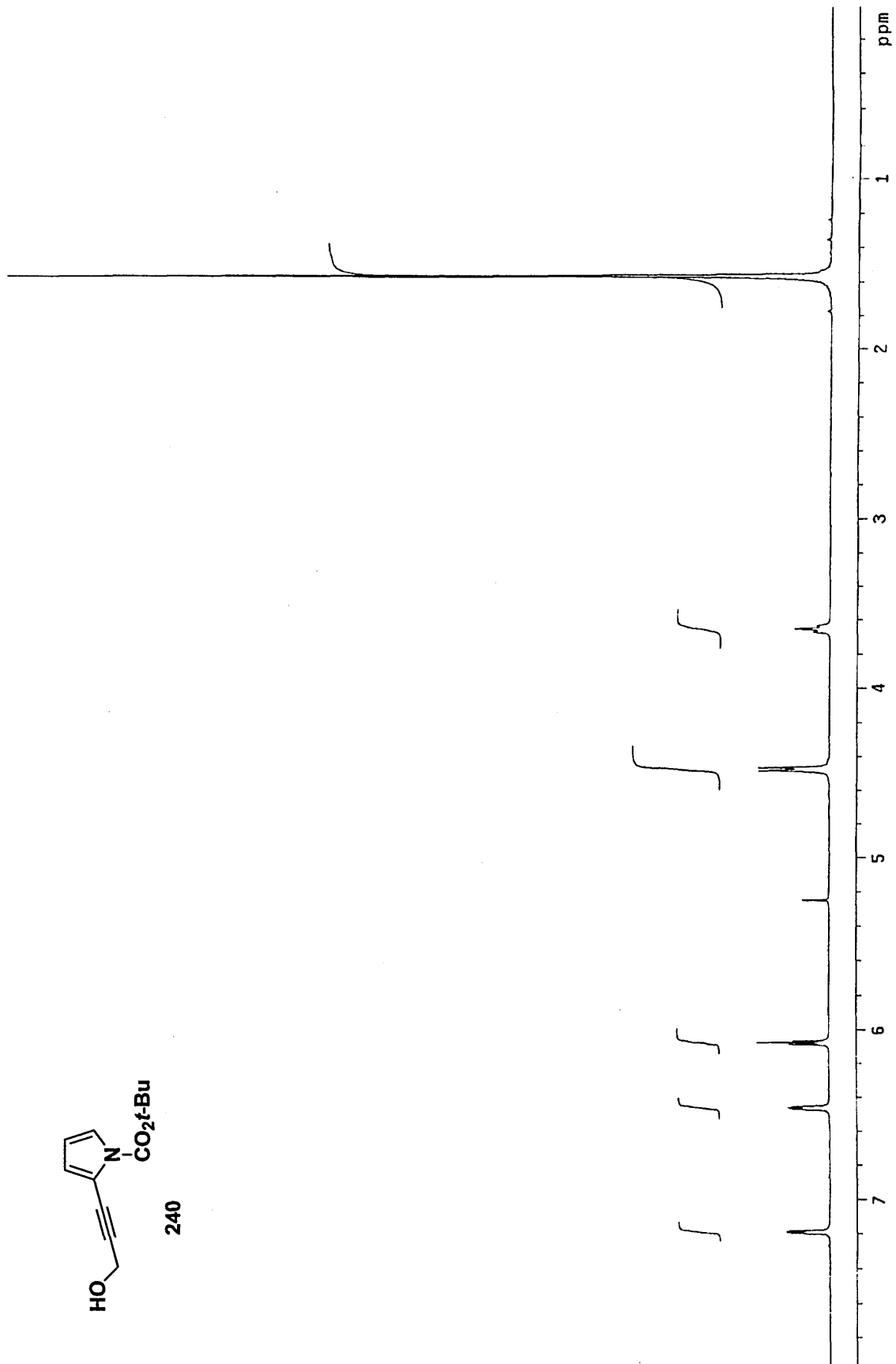


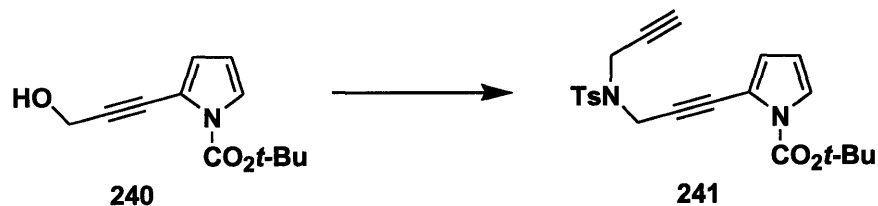


1-(t-Butoxycarbonyl)-2-(3-hydroxyprop-1-ynyl)pyrrole (240). A 50-mL, round-bottomed flask fitted with an argon inlet adapter was charged with the iodopyrrole **226** (1.811 g, 6.179 mmol), 30 mL of THF, and piperidine (3.0 mL, 2.6 g, 30 mmol). Pd(PPh₃)₂Cl₂ (0.216 g, 0.308 mmol), CuI (0.122 g, 0.642 mmol), and propargyl alcohol (0.73 mL, 0.69 g, 12 mmol) were then added, and the resulting mixture was stirred for 2 h at rt and then filtered through 10 g of silica gel with the aid of 100 mL of diethyl ether. The filtrate was concentrated under reduced pressure to yield 3.033 g of a dark red semisolid that was dissolved in 50 mL of CH₂Cl₂ and concentrated onto 6 g of silica gel which was added to the top of a column of 54 g of silica gel. Gradient elution with 10-25% EtOAc-hexanes afforded 1.185 g (87%) of **240** as a viscous honey-colored oil: IR (thin film) 3475, 2230, 1739, and 1552 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.19 (dd, *J* = 3.3, 1.6 Hz, 1 H), 6.46 (dd, *J* = 3.6, 1.6 Hz, 1 H), 6.08 (dd, *J* = 3.6, 3.3 Hz, 1 H), 4.48 (d, *J* = 5.5 Hz, 2 H), 3.65 (t, *J* = 5.5 Hz, 1 H), and 1.57 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 148.3, 122.3, 121.0, 114.6, 110.9, 91.3, 84.5, 77.3, 51.4, and 28.0; HRMS (*m/z*): [M+Na⁺] calcd for C₁₂H₁₅NO₃ 244.0944; found, 244.0937.

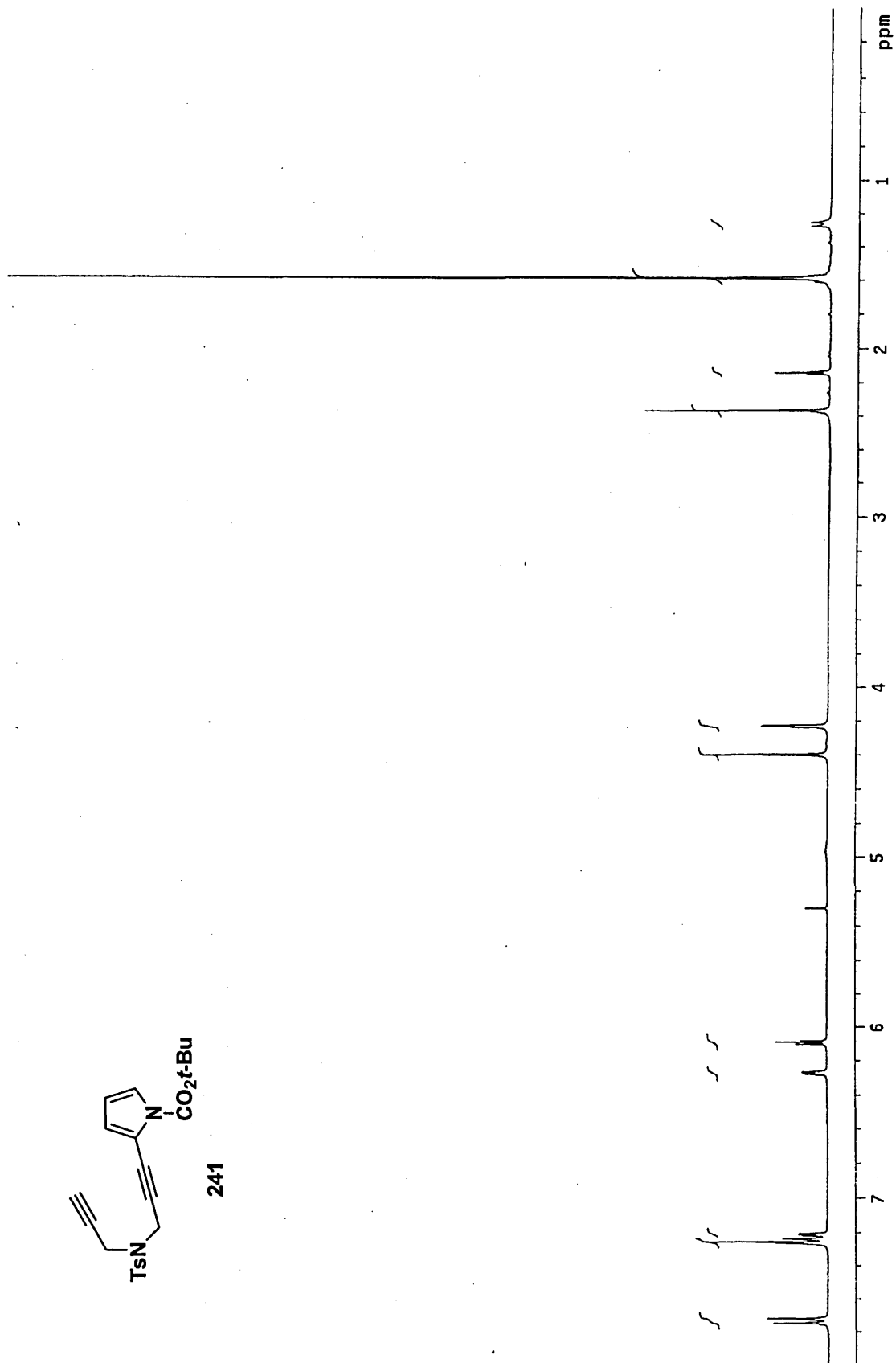
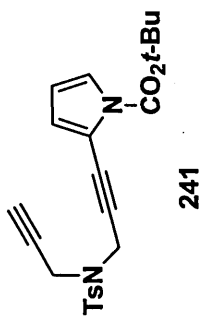


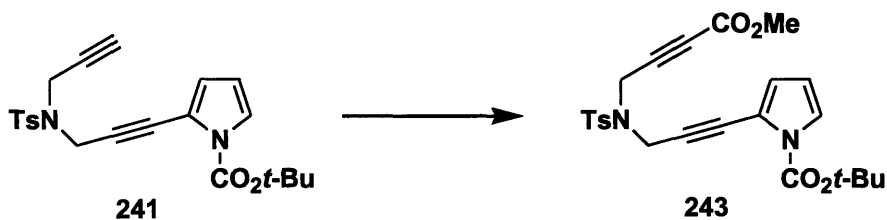
240



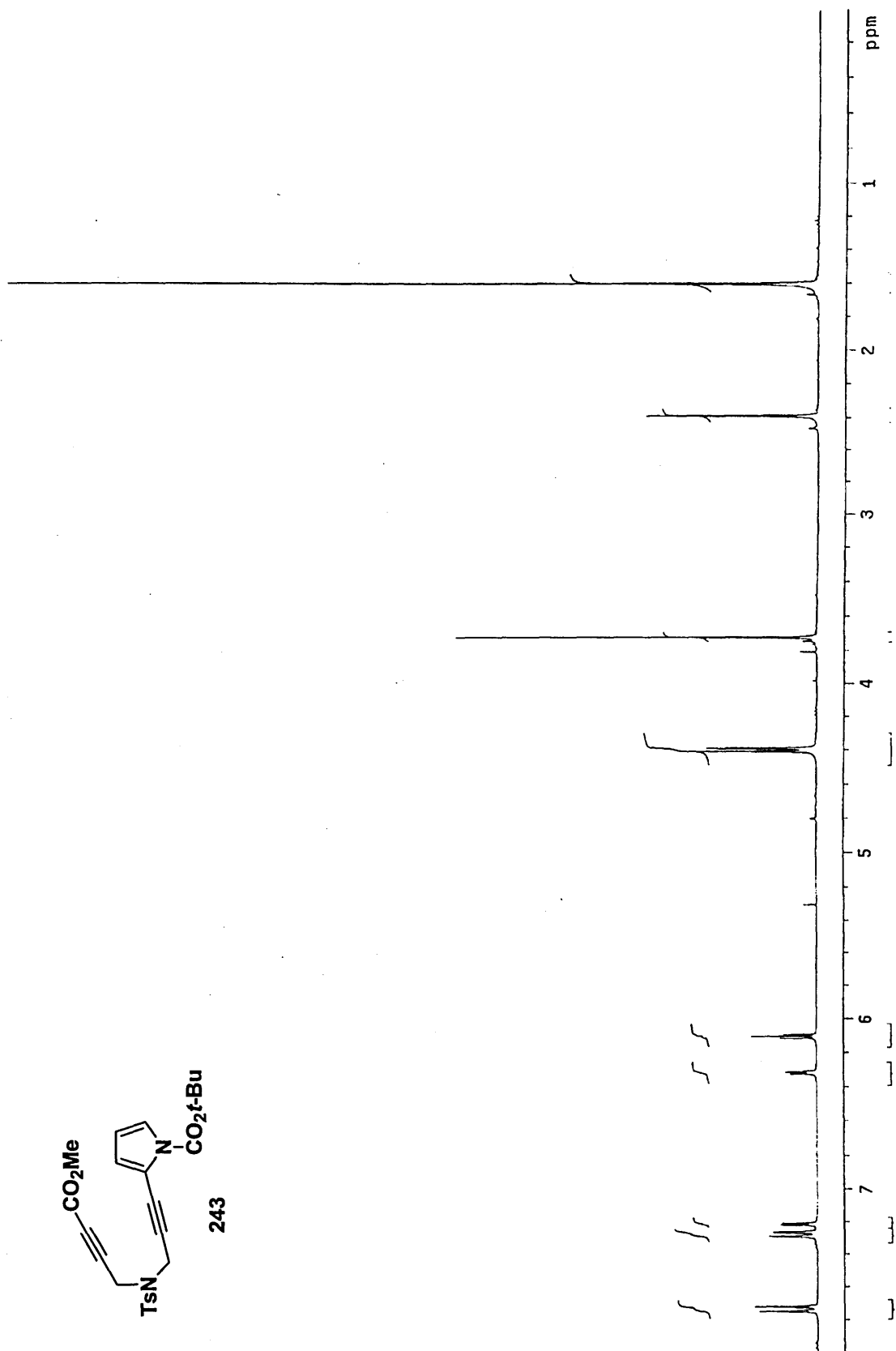
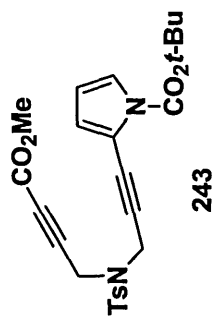


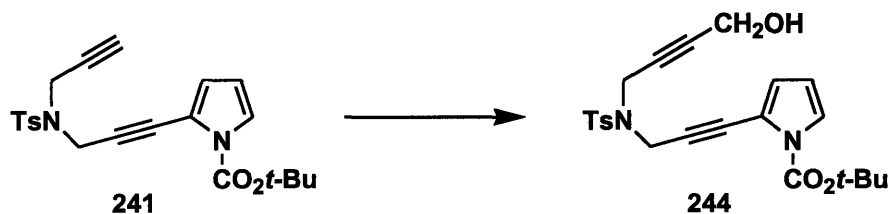
1-(*t*-Butoxycarbonyl)-2-(3-[[4-methylphenyl]sulfonyl]prop-2-ynylamino}prop-1-ynyl)pyrrole (241). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with alcohol **240** (0.514 g, 2.32 mmol), 12 mL of THF, sulphonamide **229** (0.536 g, 2.56 mmol) and triphenylphosphine (0.731 g, 2.78 mmol). Diethyl azodicarboxylate (DEAD) (0.44 mL, 0.49 g, 2.8 mmol) was added dropwise via syringe over 1 min, and the reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure to furnish 2.409 g of a brown semisolid. This material was dissolved in 100 mL of CH₂Cl₂ and concentrated onto 20 g of silica gel which was added to the top of a column of 180 g of silica gel. Gradient elution with 0-20% EtOAc-hexanes provided 0.678 g (71%) of **241** as a brown viscous oil: IR (thin film) 3288, 2234, 2123, 1733, 1598, 1551, and 1300 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, *J* = 8.2 Hz, 2 H), 7.23 (d, *J* = 8.2 Hz, 2 H), 7.20 (dd, *J* = 3.0, 1.6 Hz, 1 H), 6.26 (dd, *J* = 3.3 Hz, 1.6 Hz, 1 H), 6.08 (dd, *J* = 3.3 Hz, 3.0 Hz, 1 H), 4.40 (s, 2 H), 4.23 (d, *J* = 2.2 Hz, 2 H), 2.36 (s, 3 H), 2.18 (t, *J* = 2.2 Hz, 1 H), and 1.60 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 148.0, 143.8, 135.1, 129.4, 127.8, 122.6, 121.1, 114.1, 110.8, 85.1, 84.4, 78.3, 76.6, 74.1, 37.6, 36.5, 28.1, and 21.7; HRMS (*m/z*): [M+Na⁺] calcd for C₂₂H₂₄N₂O₄S 435.1349; found, 435.1355.



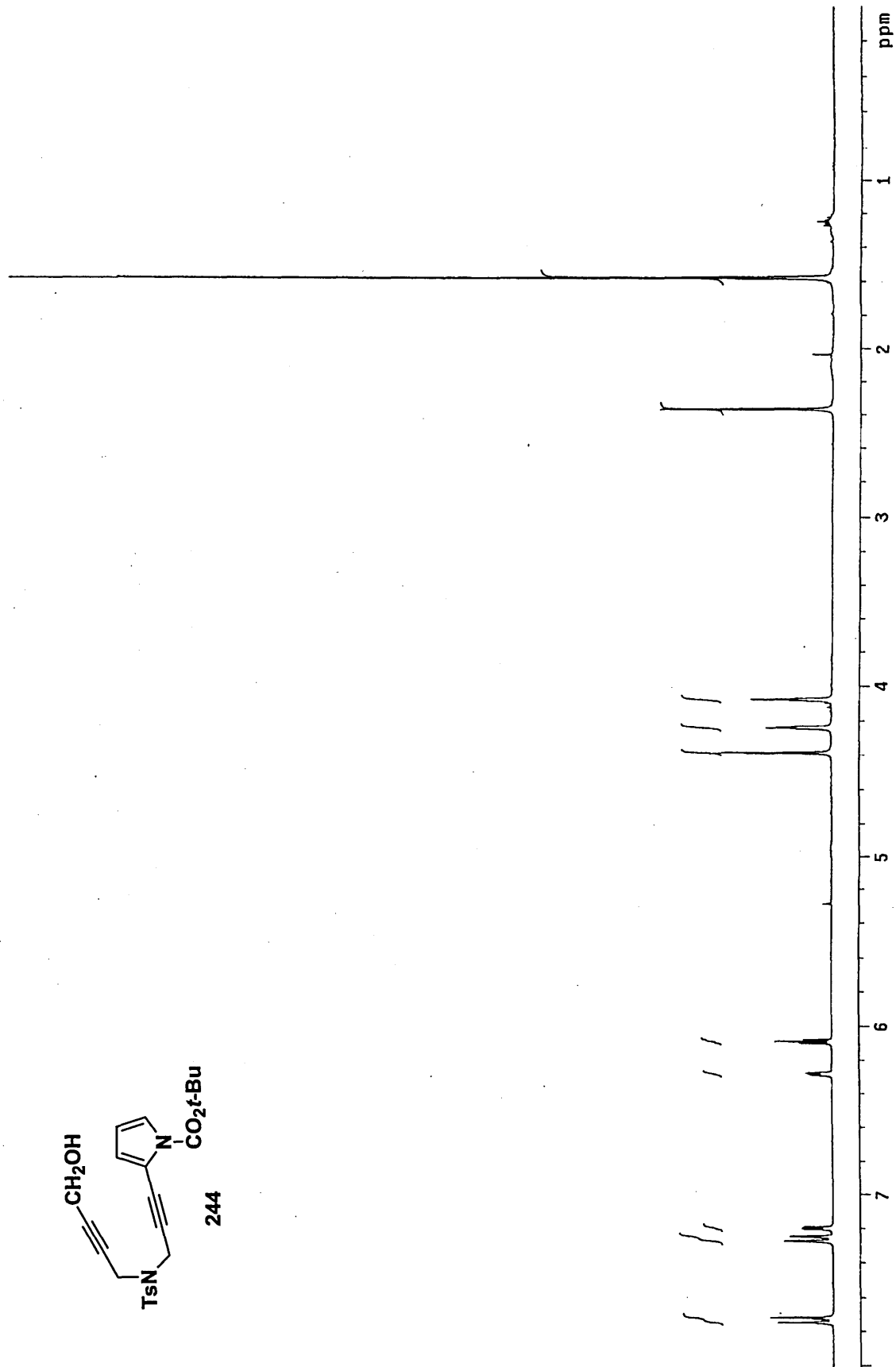
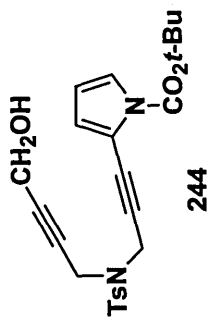


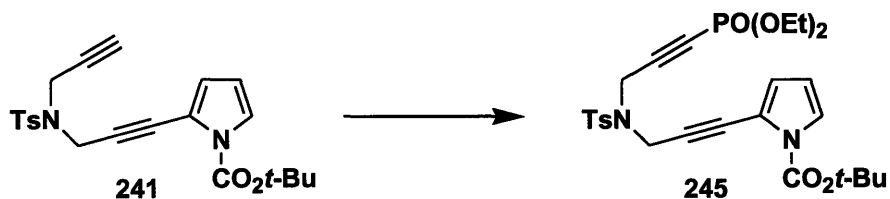
1-(*t*-Butoxycarbonyl)-2-(3-((3-methoxycarbonylprop-2-ynyl))[(4-methylphenyl)sulfonyl]amino}prop-1-ynyl)pyrrole (243). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of alkyne 241 (0.540 g, 1.31 mmol) in 7 mL of THF. The solution was cooled to 0 °C and 0.50 mL of EtMgBr solution (2.95 M in diethyl ether, 1.5 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 0 °C for 30 min, and methyl chloroformate (0.50 mL, 0.62 g, 6.6 mmol) was then added rapidly by syringe. The reaction mixture was allowed to warm to rt, stirred for 21 h, and then diluted with 10 mL of saturated aq NH₄Cl solution and 20 mL of Et₂O. The aqueous phase was separated and extracted with two 10-mL portions of Et₂O, and the combined organic phases were washed 25 mL of brine, dried over MgSO₄, filtered, and concentrated to furnish 0.714 g of a brown semisolid. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 1.5 g of silica gel which was added to the top of a column of 13.5 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes provided 0.413 g (67%) of 243 as a brown viscous oil: IR (thin film) 2242, 1744, 1720, 1598, 1551, and 1319 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.74 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 7.22 (dd, *J* = 3.3 Hz, 1.6 Hz, 1 H), 6.32 (dd, *J* = 3.6, 1.6 Hz, 1 H), 6.08 (dd, *J* = 3.6, 3.3 Hz, 1 H), 4.40 (s, 2 H), 4.21 (s, 2 H), 4.19 (s, 2 H), 3.73 (s, 3 H), 2.40 (s, 3 H), and 1.60 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 153.0, 148.0, 144.2, 134.8, 129.7, 127.9, 122.8, 121.3, 114.1, 110.9, 84.8, 84.6, 80.8, 78.9, 77.1, 53.0, 38.3, 36.6, 28.2, and 21.8; HRMS (*m/z*): [M+Na⁺] calcd for C₂₄H₂₆N₂O₆S 493.1404; found, 493.1401.



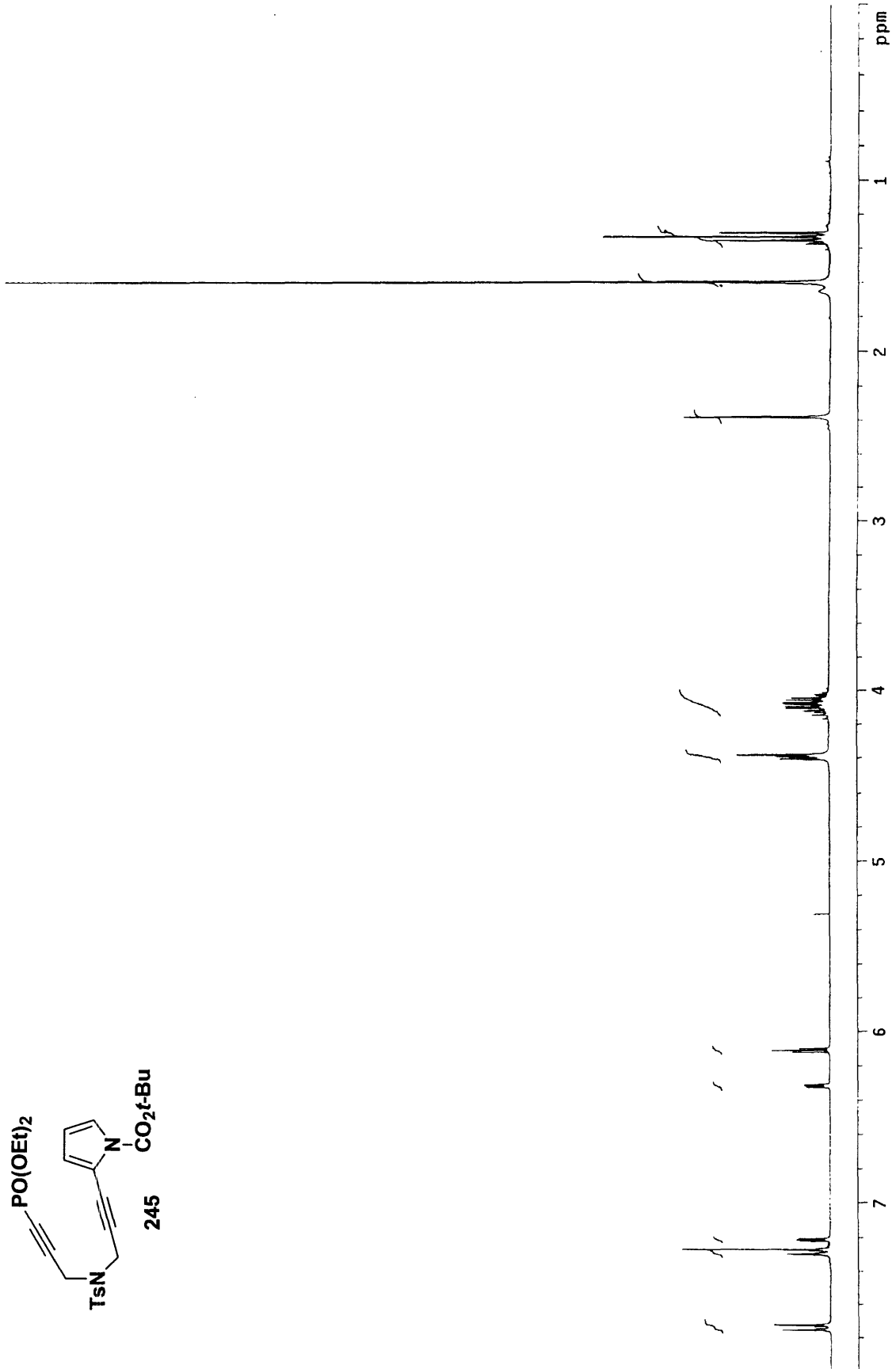
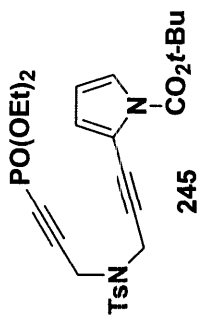


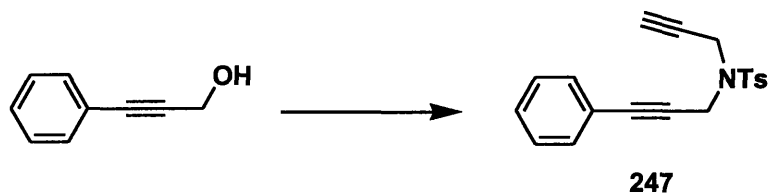
1-(*t*-Butoxycarbonyl)-2-(3-((4-hydroxybut-2-ynyl)[(4-methylphenyl)sulfonyl]amino}prop-1-ynyl)pyrrole (**244**). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with paraformaldehyde (0.120 g, 3.99 mmol) and the flask was cooled to 0 °C. A 25-mL, pear-shaped flask fitted with a rubber septum and argon inlet needle was charged with the alkyne **241** (0.781 g, 1.89 mmol) and 8 mL of THF, and the resulting solution was cooled at 0 °C while 0.65 mL of EtMgBr solution (3.0 M in diethyl ether, 2.0 mmol) was added dropwise by syringe over 1 min. The resulting mixture was stirred at 0 °C for 30 min and then was transferred via cannula into the flask containing the paraformaldehyde. The reaction mixture was allowed to warm to rt, stirred for 60 h, and then diluted with 10 mL of saturated aq NH₄Cl solution, 5 mL of water, and 20 mL of Et₂O. The aqueous phase was separated and extracted with three 10-mL portions of Et₂O, and the combined organic phases were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to furnish 0.819 g of a honey-colored oil. This material was dissolved in CH₂Cl₂ and concentrated onto 10 g of silica gel which was added to the top of a column of 90 g of silica gel. Gradient elution with 0-50% EtOAc-hexanes provided 0.297 g (47%) of **244** as a light-brown oil: IR (thin film) 3524, 2981, 2234, 1743, 1598, 1551, 1140, and 1071cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.74 (d, *J* = 8.3 Hz, 2 H), 7.26 (d, *J* = 8.3 Hz, 2 H), 7.20 (dd, *J* = 3.3, 1.7 Hz, 1 H), 6.28 (dd, *J* = 3.5, 1.7 Hz, 1 H), 6.09 (dd, *J* = 3.5, 3.3 Hz, 1 H), 4.39 (s, 2 H), 4.28-4.21 (m, 2 H), 4.10-4.05 (m, 2 H), 2.37 (s, 3 H), and 1.58 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 148.2, 144.0, 135.4, 129.6, 128.1, 122.8, 121.3, 114.3, 111.0, 85.4, 84.6, 84.3, 78.5, 78.2, 50.9, 37.9, 36.9, 28.1, and 21.6; HRMS (*m/z*): [M+Na⁺] calcd for C₂₃H₂₆N₂O₅S 465.1455; found, 465.1469.



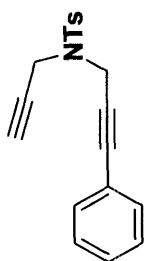


1-(*t*-Butoxycarbonyl)-2-(3-[3-{bisethoxyphosphoryl}prop-2-ynyl])[(4-methylphenyl)sulfonyl]amino}prop-1-ynyl)pyrrole (**245**). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with the alkyne **241** (0.597 g, 1.448 mmol) and 7 mL of THF. The solution was cooled to 0 °C and 0.54 mL of EtMgBr solution (2.95 M in diethyl ether, 1.6 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 0 °C for 30 min, and diethyl chlorophosphonate (1.05 mL, 1.26 g, 7.30 mmol) was then added rapidly by syringe. The reaction mixture was allowed to warm to rt, stirred for 18 h, and then diluted with 10 mL of saturated aq NH₄Cl solution and 20 mL of Et₂O. The aqueous phase was separated and extracted with two 10-mL portions of Et₂O, and the combined organic phases were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to furnish 0.872 g of a light-brown oil. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 3 g of silica gel which was added to the top of a column of 27 g of silica gel. Gradient elution with 30-50% EtOAc-hexanes provided 0.589 g (74%) of **245** as a light-brown oil: IR (thin film) 2210, 1747, 1598, 1551, and 1264 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.74 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 7.21 (dd, *J* = 3.3, 1.6 Hz, 1 H), 6.32 (dd, *J* = 3.6, 1.6 Hz, 1 H), 6.11 (dd, *J* = 3.6, 3.3 Hz, 1 H), 4.40 (d, *J* = 4.1 Hz, 2 H), 4.38 (s, 2 H), 4.17-4.00 (m, 4 H), 2.38 (s, 3 H), 1.59 (s, 9 H), and 1.41-1.27 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 148.0, 144.4, 134.9, 129.9, 127.9, 122.8, 121.3, 114.0, 111.0, 93.9, 93.3, 84.6, 84.5, 78.9, 63.4, 63.3, 38.1, 36.8, 28.0, 21.6, 16.2, and 16.1; HRMS (*m/z*): [M+Na⁺] calcd for C₂₆H₃₃N₂O₇PS 571.1638; found, 571.1631.

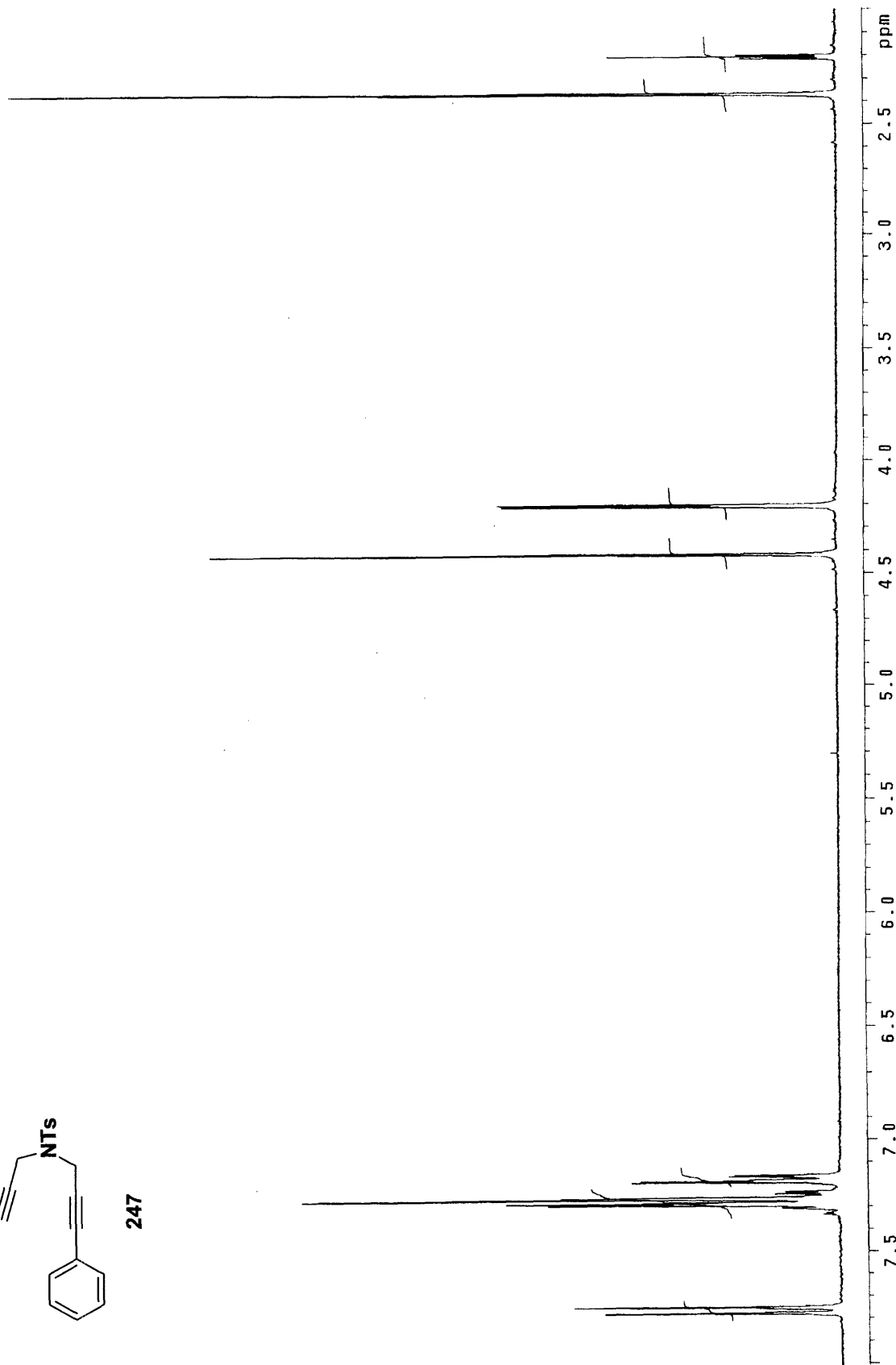


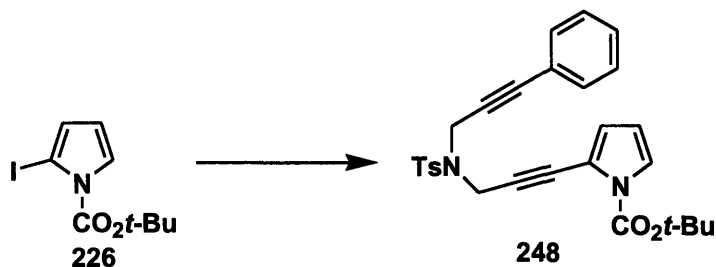


3-[[4-(4-Methylphenyl)sulfonyl]prop-2-ynylamino]prop-1-ynylbenzene (247). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of the alcohol (0.400 g, 3.03 mmol) in 15 mL of THF, triphenylphosphine (0.876 g, 3.34 mmol), *N*-tosylpropargylamine (**229**) (0.674 g, 3.22 mmol) and diisopropyl azodicarboxylate (0.66 mL, 0.68 g, 3.35 mmol). The reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure to furnish 3.077 g of a brown semisolid that was dissolved in 50 mL of CH₂Cl₂ and concentrated onto 10 g of silica gel which was added to the top of a column of 200 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes provided 0.865 g (88%) of sulfonamide **247** as a light-yellow solid: mp 73-74 °C; IR (thin film) 3276, 2240, 2126, 1597, and 1349 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.77 (d, *J* = 8.3 Hz, 2 H), 7.27 (m, 5 H), 7.18 (m, 2 H), 4.42 (s, 2 H), 4.21 (d, *J* = 2.5 Hz, 2 H), 2.37 (s, 3 H), and 1.08 (t, *J* = 2.5 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 144.1, 135.2, 131.7, 129.7, 128.6, 128.2, 128.0, 122.1, 86.0, 81.3, 76.5, 74.2, 37.2, 36.6, and 21.5; HRMS (*m/z*): [M+Na⁺] calcd for C₁₉H₁₇NO₂S 346.0872; found, 346.0861.

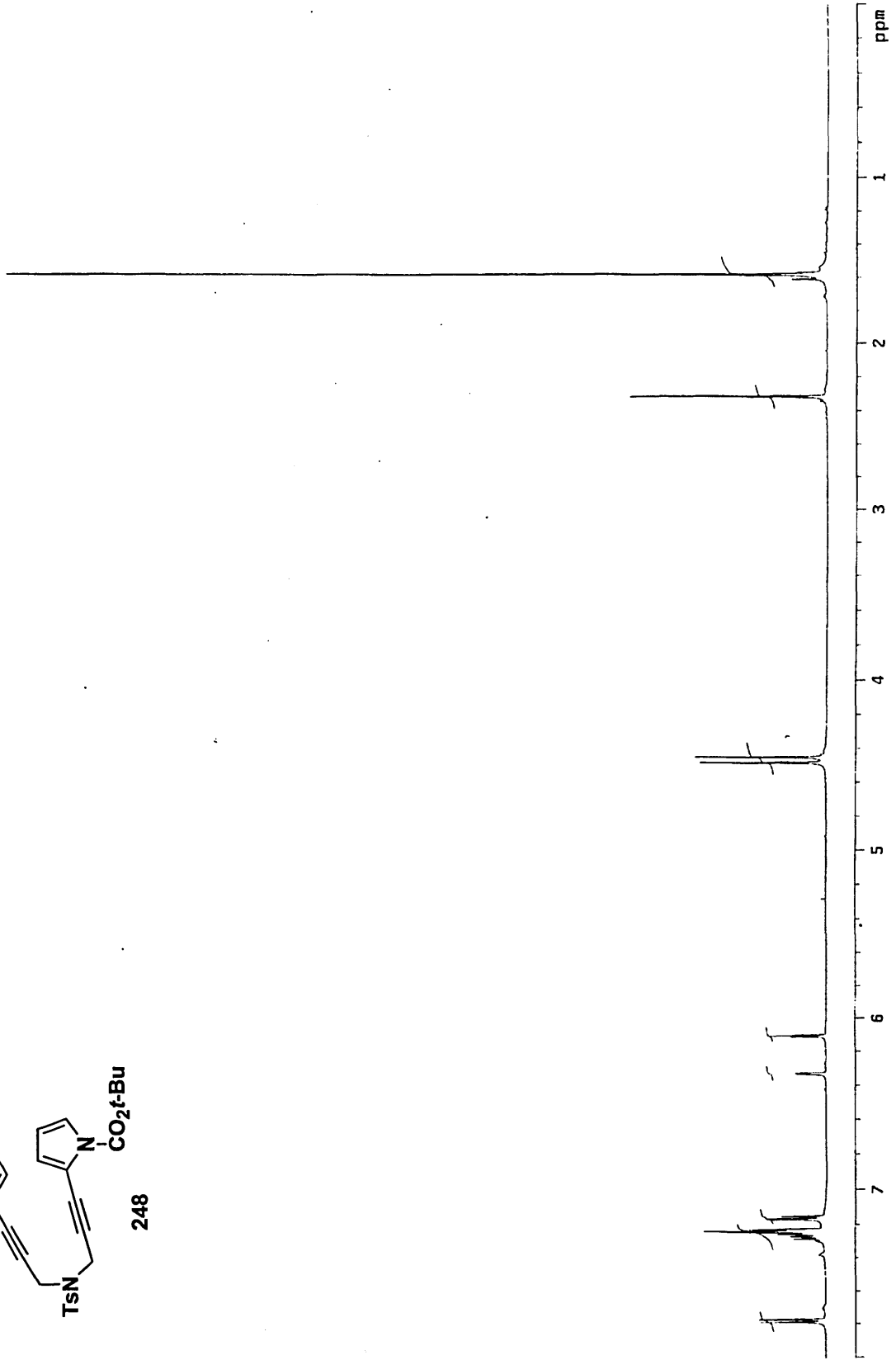
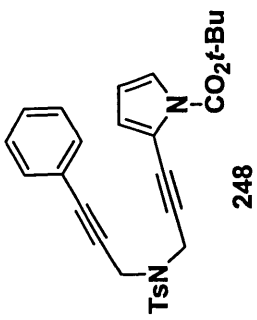


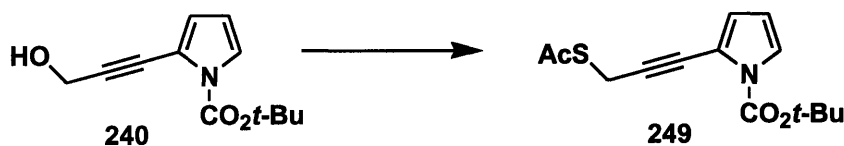
247



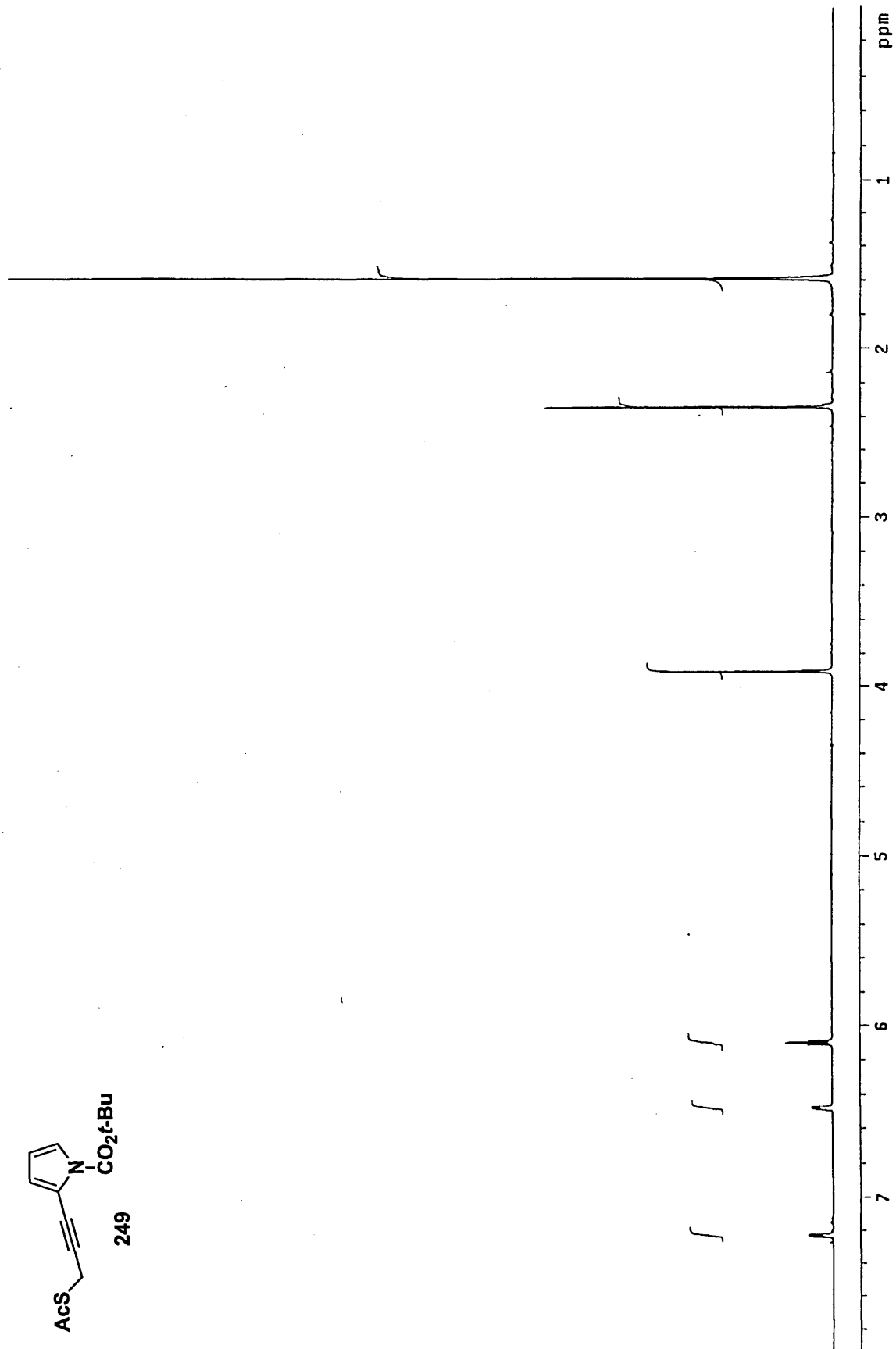
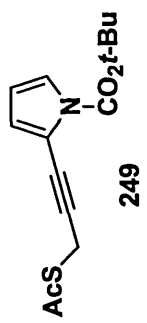


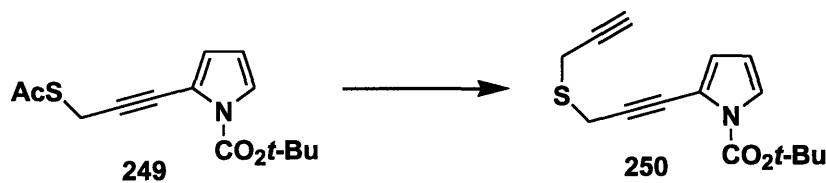
1-(*t*-Butoxycarbonyl)-2-(3-{{[(4-methylphenyl)sulfonyl]}(3-phenylprop-2-ynyl)amino}prop-1-ynyl)-pyrrole (248). A 25-mL, round-bottomed flask fitted with an argon inlet adapter was charged with iodopyrrole 226 (0.629 g, 2.15 mmol), 10 mL of THF, and piperidine (0.80 mL, 0.78 g, 9.2 mmol). Pd(Ph₃P)₂Cl₂ (0.075 g, 0.11 mmol), CuI (0.068 g, 0.36 mmol), and alkyne 247 (0.588 g, 1.82 mmol) were then added, and the resulting mixture was stirred for 3 h at rt and then filtered through 10 g of silica gel in a sintered glass funnel washing with 100 mL of diethyl ether. The filtrate was concentrated under reduced pressure to yield 1.139 g of a dark red semisolid that was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 3 g of silica gel which was added to the top of a column of 100 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes afforded 0.394 g (44%) of pyrrole 248 product as a viscous honey-colored oil: IR (thin film) 2236, 1748, 1598, 1551, and 1323cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.79 (d, *J* = 8.2 Hz, 2 H), 7.26 (m, 6 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 6.34 (dd, *J* = 3.4, 1.7 Hz, 1 H), 6.11 (dd, *J* = 3.4, 3.4 Hz, 1 H), 4.49 (s, 2 H), 4.45 (s, 2 H), 2.32 (s, 3 H), and 1.58 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 151.3, 148.2, 143.9, 135.5, 131.7, 129.7, 128.6, 128.3, 128.1, 122.8, 122.4, 121.4, 114.3, 110.9, 85.5, 84.5, 81.8, 78.3, 38.0, 37.5, 28.1, and 21.6; HRMS (*m/z*): [M+Na⁺] calcd for C₂₈H₂₈N₂O₄S 511.1662; found, 511.1684.





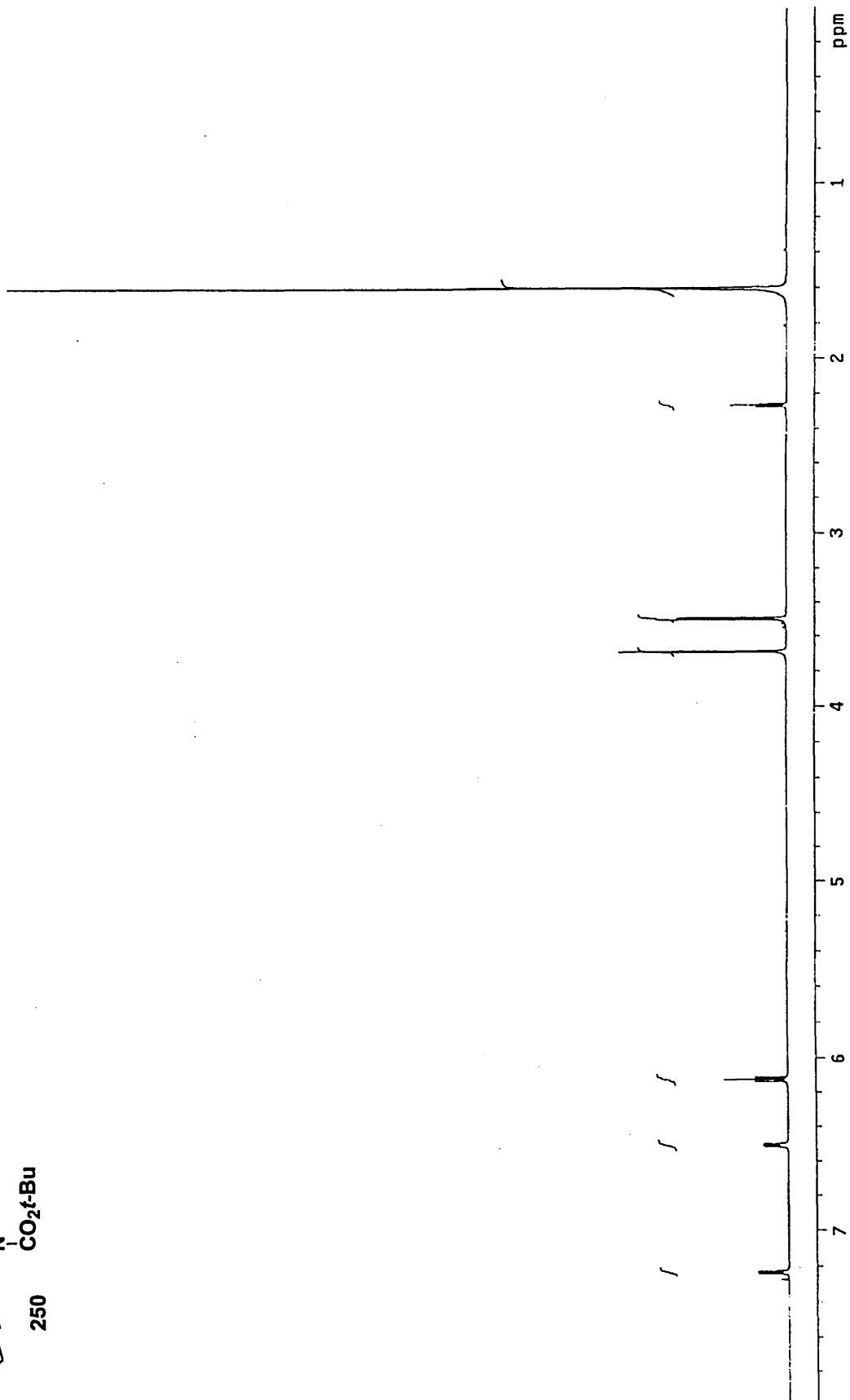
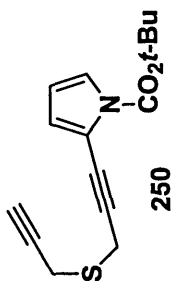
1-(*t*-Butoxycarbonyl)-2-(3-[acetylthio]prop-1-ynyl)pyrrole (249). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with the alcohol **240** (0.396 g, 1.79 mmol) and 15 mL of benzene. Thiolacetic acid (0.13 mL, 0.14 g, 1.8 mmol) was added dropwise via syringe over 1 min and the resulting solution was cooled to 0 °C. A 10-mL, pear-shaped flask was charged with 8 mL of benzene, triphenylphosphine (0.47 g, 1.8 mmol), and diethyl azodicarboxylate (DEAD) (0.30 mL, 0.34 g, 1.9 mmol), and the resulting solution was stirred at 0 °C for 15 min and then transferred via cannula into the first solution over 2 min (2-mL benzene rinse). The ice bath was removed and the reaction mixture was stirred for 2 h and then concentrated under reduced pressure to furnish 1 g of a brown semisolid. This material was dissolved in 50 mL of CH₂Cl₂ and concentrated onto 5 g of silica gel which was added to the top of a column of 45 g of silica gel. Elution with toluene provided 0.334 g (67%) of **249** as a light yellow oil: IR (thin film) 2237, 1743, 1694, and 1552 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.23 (dd, *J* = 3.3, 1.7 Hz, 1 H), 6.48 (dd, *J* = 3.5, 1.7 Hz, 1 H), 6.10 (dd, *J* = 3.5, 3.3 Hz, 1 H), 3.91 (s, 2 H), 2.34 (s, 3 H), and 1.59 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 194.0, 148.4, 122.5, 121.3, 114.7, 111.0, 87.4, 84.3, 75.3, 30.2, 28.0, and 19.1; HRMS (*m/z*): [M+Na⁺] calcd for C₁₄H₁₇NO₃S 302.0821; found, 302.0819.

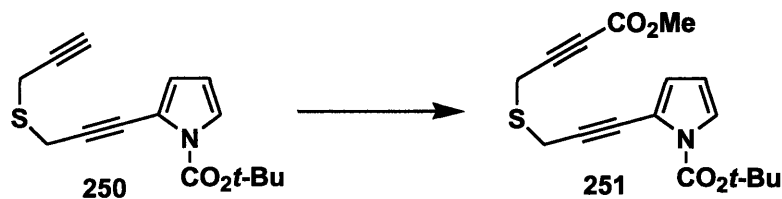




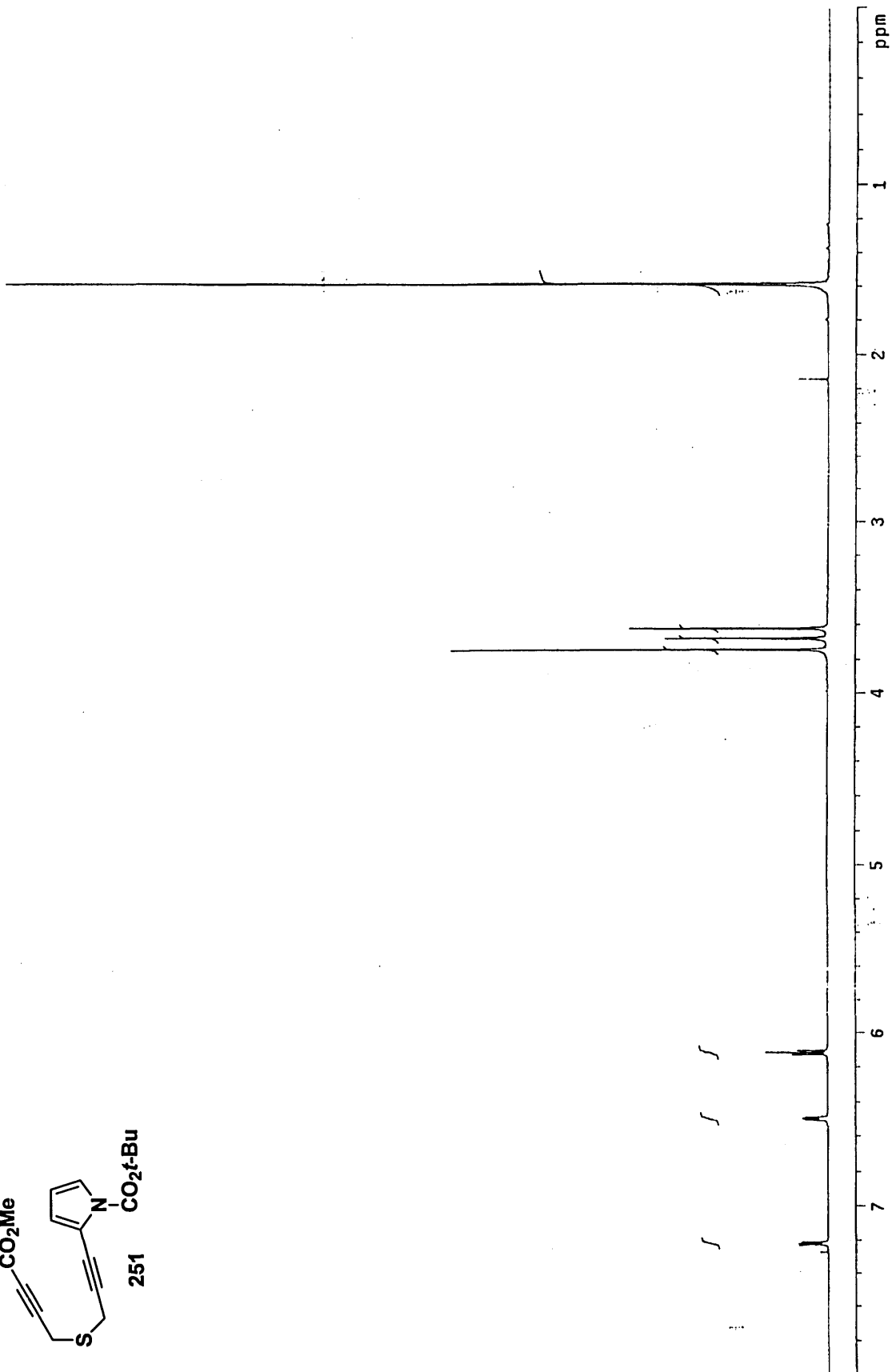
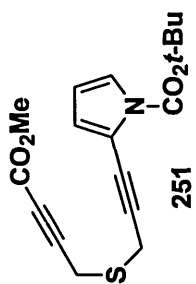
1-(*t*-Butoxycarbonyl)-2-(3-[prop-2-ynylthio]prop-1-ynyl)pyrrole

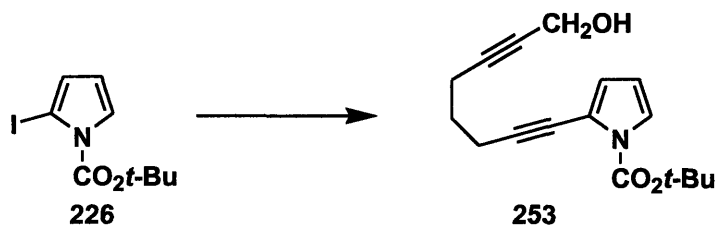
(250). A 10-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with the thiol ester **249** (0.312 g, 1.12 mmol), 3 mL of methanol, Na₂S₂O₃·5H₂O (0.003 g, 0.01 mmol), and KOH (88% pellets, 0.065 g, 1.2 mmol). The resulting solution was cooled to 0 °C, stirred for 30 min, and 0.13 mL of propargyl bromide solution (80% w/w in toluene, 0.13 g, 1.1 mmol) was then added dropwise via syringe over 1 min. The ice bath was removed and the reaction mixture was stirred for 1 h, diluted with 3 mL of water, and then the methanol was evaporated under reduced pressure. The residue was extracted with three 5-mL portions of diethyl ether and the combined organic phases were dried over MgSO₄, filtered, and concentrated to furnish 0.342 g of a light brown oil. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 3 g of silica gel which was added to the top of a 27-g column of silica gel. Gradient elution with 0-1% EtOAc-hexanes provided 0.216 g (70%) of **250** as a light yellow oil: IR (thin film) 3290, 2233, 2118, 1741, and 1551 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.23 (dd, *J* = 3.3, 1.7 Hz, 1 H), 6.50 (dd, *J* = 3.6, 1.7 Hz, 1 H), 6.12 (dd, *J* = 3.6, 3.3 Hz, 1 H), 3.69 (s, 2 H), 3.50 (d, *J* = 2.5 Hz, 2 H), 2.27 (t, *J* = 2.5 Hz, 1 H), and 1.60 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 148.4, 122.4, 121.0, 114.9, 111.0, 88.1, 84.3, 79.6, 75.8, 71.4, 28.1, 20.5, and 19.0 ; HRMS (*m/z*): [M+Na⁺] calcd for C₁₅H₁₇NO₂S 298.0872; found, 298.0878.



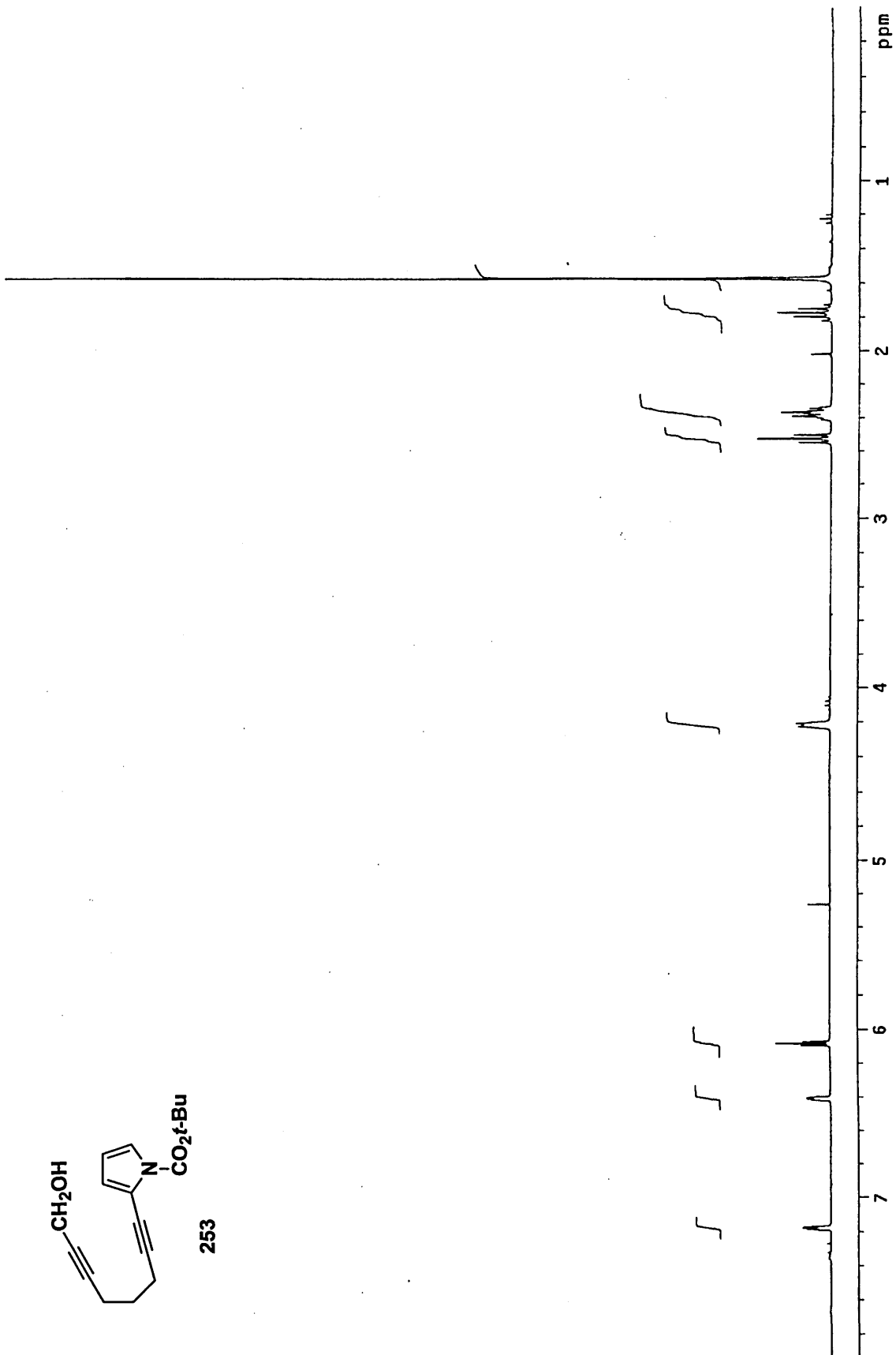
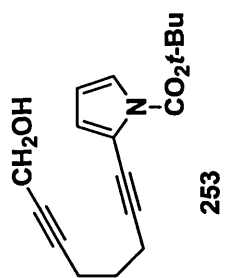


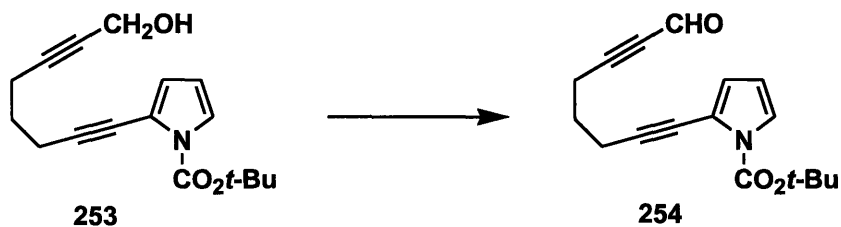
1-(*t*-Butoxycarbonyl)-2-(3-[3-{carbomethoxy}prop-2-ynylthio]prop-1-ynyl)pyrrole (251). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with the alkyne **250** (0.210 g, 0.762 mmol) and 4 mL of THF. The solution was cooled to 0 °C and 0.31 mL of EtMgBr solution (2.95 M in diethyl ether, 0.91 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 0 °C for 30 min, and methyl chloroformate (0.30 mL, 0.37 g, 3.9 mmol) was then added rapidly by syringe. The reaction mixture was allowed to warm to rt, stirred for 18 h, and then diluted with 10 mL of saturated aq NH₄Cl solution and 20 mL of Et₂O. The aqueous phase was separated and extracted with three 10-mL portions of Et₂O, and the combined organic phases were dried over MgSO₄, filtered, and concentrated to furnish 0.215 g of a yellow oil. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 3 g of silica gel which was added to the top of a column of 27 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes provided 0.164 g (65%) of **251** as a light-yellow oil: IR (thin film) 2238, 1721, and 1551 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.22 (dd, *J* = 3.3, 1.6 Hz, 1 H), 6.50 (dd, *J* = 3.6, 1.6 Hz, 1 H), 6.12 (dd, *J* = 3.6, 3.3 Hz, 1 H), 3.74 (s, 3 H), 3.68 (s, 2 H), 3.62 (s, 2 H), and 1.59 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 153.8, 148.3, 122.5, 121.03, 114.7, 111.0, 87.5, 84.4, 84.2, 76.3, 74.6, 52.8, 28.0, 20.8, and 18.7; HRMS (*m/z*): [M+Na⁺] calcd for C₁₇H₁₉NO₄S 356.0927; found, 356.0940.



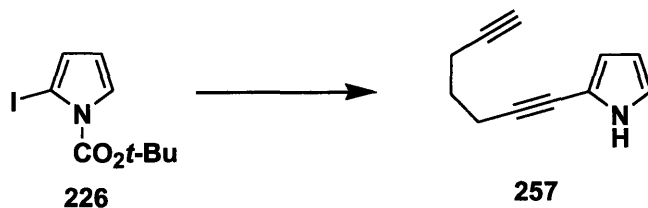


1-(*t*-Butoxycarbonyl)-2-(8-hydroxyocta-1,6-diynyl)pyrrole (253). A 50-mL, round-bottomed flask fitted with an argon inlet adapter was charged with iodopyrrole **226** (1.811 g, 6.180 mmol), 30 mL of THF, and piperidine (3.0 mL, 2.6 g, 30 mmol). Pd(PPh₃)₂Cl₂ (0.215 g, 0.306 mmol), CuI (0.216 g, 1.14 mmol), and alcohol **252** (0.744g, 6.09 mmol) were then added, and the resulting mixture was stirred for 2 h at rt and then filtered through 10 g of silica gel with the aid of 100 mL of diethyl ether. The filtrate was concentrated to yield 3.117 g of a dark red semisolid that was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 5 g of silica gel which was added to the top of a column of 80 g of silica gel. Gradient elution with 0-20% EtOAc-hexanes afforded 1.128 g (64%) of **253** as a viscous light-yellow oil: IR (thin film) 3409, 2285, 2225, 1739, and 1552 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.19 (dd, *J* = 3.3, 1.6 Hz, 1 H), 6.41 (dd, *J* = 3.6, 1.6 Hz, 1 H), 6.08 (dd, *J* = 3.6, 3.3 Hz, 1 H), 4.25-4.20 (m, 2 H), 2.53 (t, *J* = 7.0 Hz, 2 H), 2.43-2.32 (m, 3 H), 1.78 (quint, *J* = 7.0 Hz, 2 H), and 1.58 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 148.6, 121.8, 120.0, 115.7, 110.8, 92.7, 85.2, 84.1, 79.2, 73.3, 51.2, 28.0, 27.7, 19.0, and 18.0; HRMS (*m/z*): [M+Na⁺] calcd for C₁₇H₂₁NO₃ 310.1414; found, 310.1426.

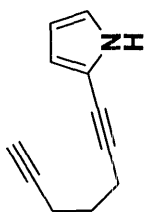




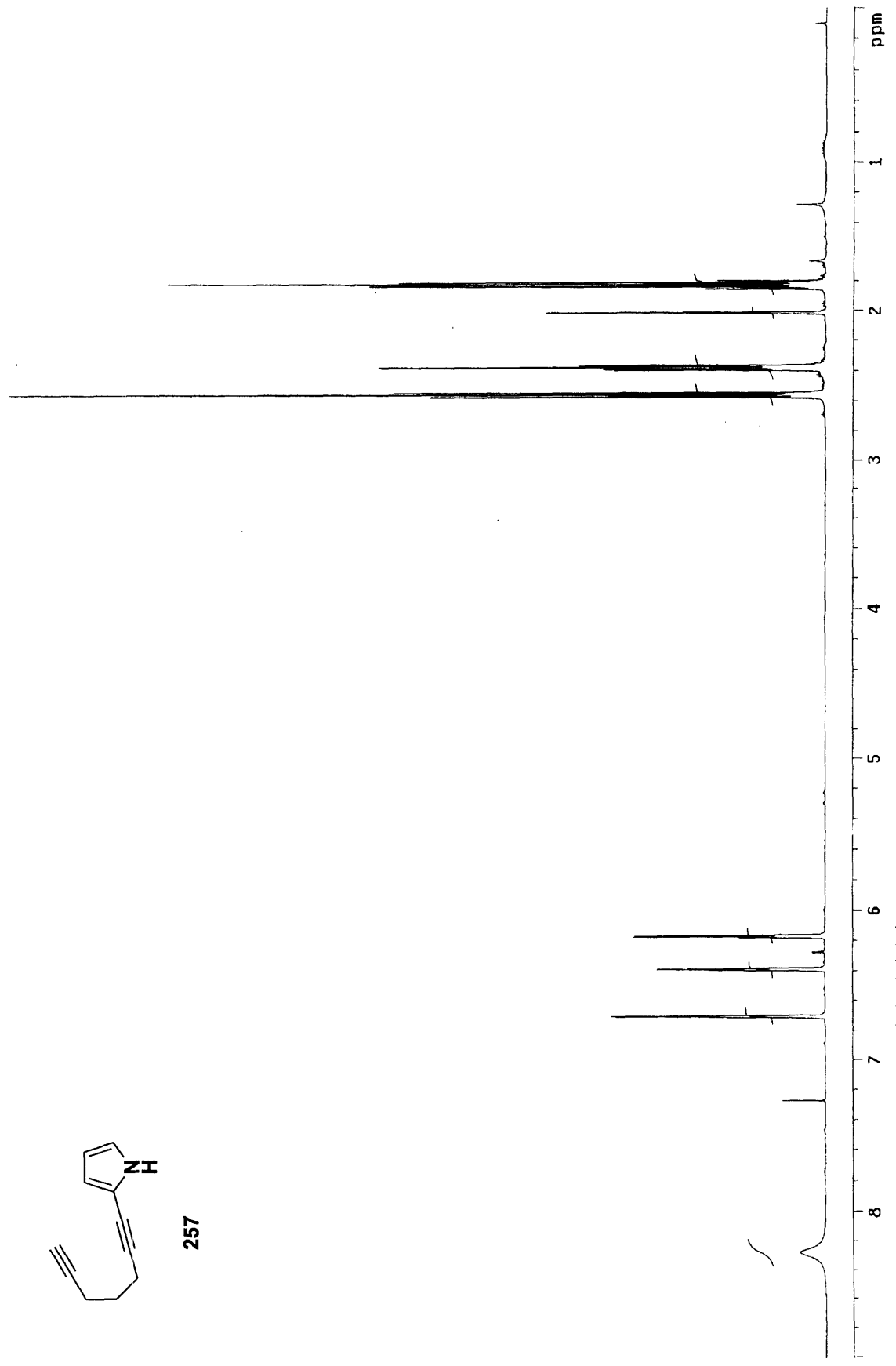
1-(*t*-Butoxycarbonyl)-2-(8-oxoocta-1,6-diyne)pyrrole (254). A 50-mL, round-bottomed flask fitted with an argon inlet adapter was charged with the alcohol **253** (1.121 g, 3.900 mmol), 30 mL of CH₂Cl₂, and Dess-Martin periodinane (2.481 g, 5.850 mmol). After stirring at rt for 2 h, the reaction mixture was vacuum-filtered through 15 g of silica gel with the aid of 20% EtOAc-hexanes. Concentration of the filtrate provided 1.005 g (90%) of **254** as a viscous light-yellow oil: IR (film) 2275, 2202, 1740, 1668, and 1552 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.18 (s, 1 H), 7.21 (dd, *J* = 3.4, 1.7 Hz, 1 H), 6.45 (dd, *J* = 3.4, 1.7 Hz, 1 H), 6.12 (dd, *J* = 3.4, 3.4 Hz, 1 H), 2.66 (t, *J* = 6.9 Hz, 2 H), 2.57 (t, *J* = 6.9 Hz, 2 H), 1.90 (quint, *J* = 6.9 Hz, 2 H), and 1.61 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 177.3, 148.5, 122.1, 120.2, 115.5, 110.9, 98.4, 91.8, 84.2, 82.1, 74.1, 28.2, 26.8, 19.2, and 18.4; HRMS (*m/z*): [M+Na⁺] calcd for C₁₇H₁₉NO₃, 308.1257; found, 308.1268.

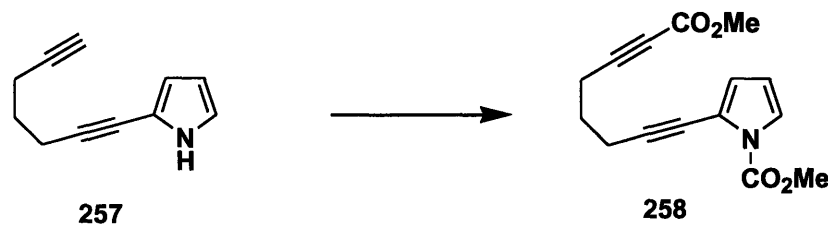


2-(hept-1,6-diyndyl)pyrrole (257). A 250-mL, round-bottomed flask fitted with an argon inlet adapter was charged with iodopyrrole **226** (5.864 g, 20.00 mmol), 100 mL of THF, and piperidine (9.0 mL, 8.8 g, 103 mmol). Pd(PPh₃)₂Cl₂ (0.712 g, 1.01 mmol), CuI (0.463 g, 2.43 mmol), and alkyne **259** (5.0 mL, 4.0 g, 43 mmol) were then added, and the resulting mixture was stirred for 4 h at rt and then filtered through 10 g of silica gel with the aid of 200 mL of hexanes. The filtrate was concentrated and immediately dissolved in 100 mL of THF in a 250-mL round-bottomed flask fitted with an argon inlet adapter. To this solution was added 14 mL of sodium methoxide solution (4.4 M in MeOH, 61 mmol) and the resulting mixture was stirred at rt for 1 hr. The reaction mixture was then diluted with 300 mL of ether and 200 mL of water, and the organic phase was separated and washed with 200 mL of water. The combined aqueous phases were extracted with three 200-mL portions of ether, and the combined organic phases were dried over MgSO₄, filtered, and concentrated to give 7.357 g of a dark-brown oil that was added to the top of a 200-g column of silica gel and eluted with 0-5% EtOAc-hexanes to furnish 1.369 g (44%) of **257** as a light-brown oil: IR (thin film) 3407, 3292, 2226, 2116 and 1555 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.31 (s, 1 H), 6.70 (dd, *J* = 4.1, 2.8 Hz, 1 H), 6.41 (dd, *J* = 6.1, 2.8 Hz, 1 H), 6.18 (dd, *J* = 6.1, 4.1 Hz, 1 H), 2.57 (t, *J* = 7.0 Hz, 2 H), 2.39 (td, *J* = 7.0, 2.6 Hz, 1 H), 2.04 (t, *J* = 2.6 Hz, 1 H), and 1.83 (quint, *J* = 7.0 Hz, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 118.9, 113.8, 113.4, 109.0, 89.9, 83.7, 73.7, 69.2, 27.7, 18.6, and 17.7; HRMS (*m/z*): [M-H]⁻ calcd for C₁₁H₁₁ 156.0808; found, 156.0803.



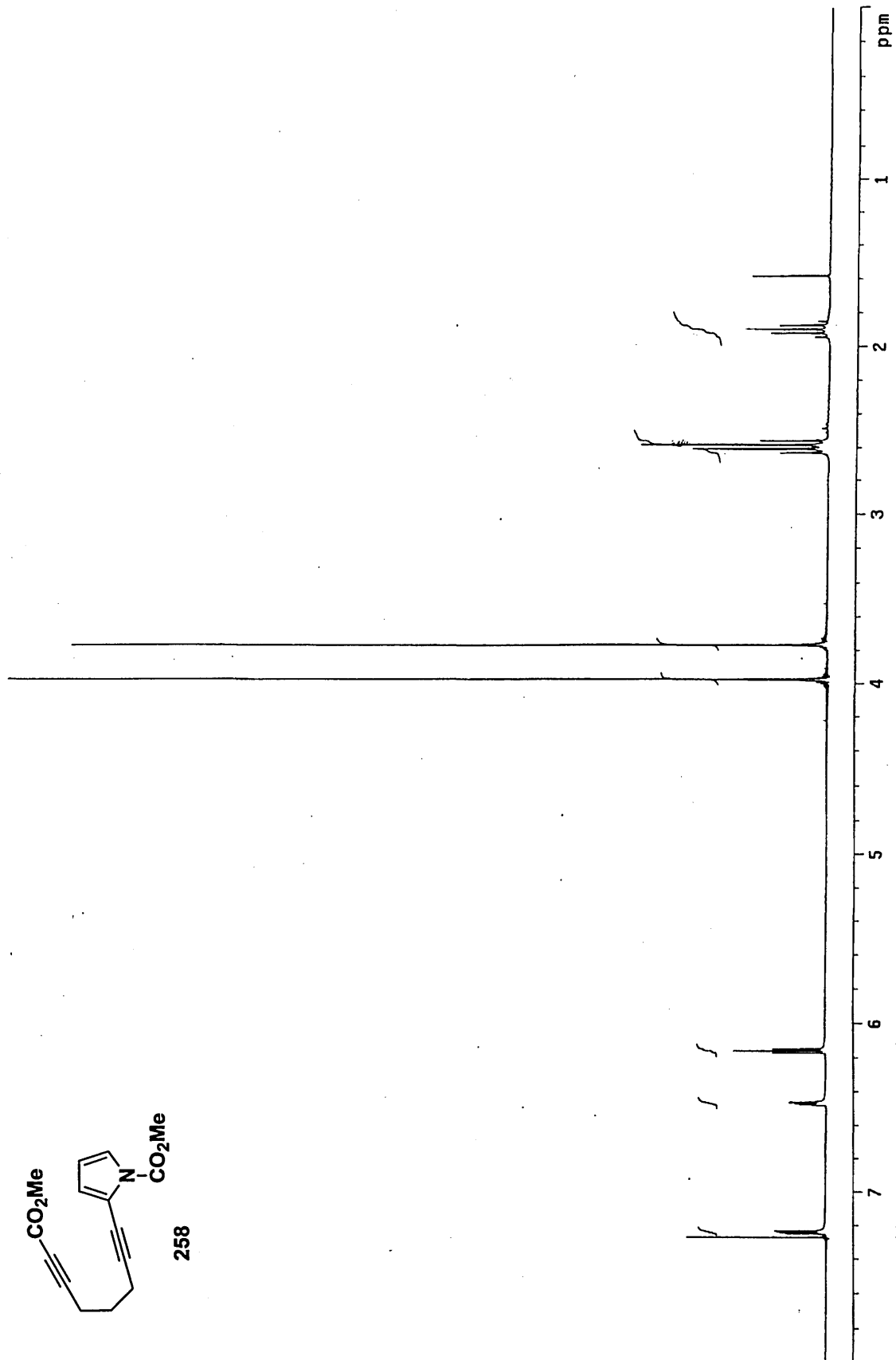
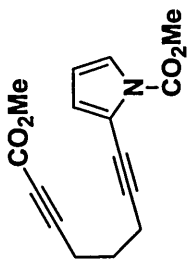
257

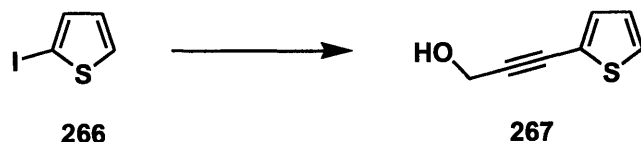




1-(Carbomethoxy)-2-(7-[carbomethoxy]hept-1,6-diynyl)pyrrole

(258). A 25-mL pear-shaped flask fitted with a rubber septum and argon inlet needle was charged with alkynyl pyrrole **257** (0.374 g, 2.38 mmol) and 20 mL of Et₂O. The solution was cooled to -78 °C and then 2.3 mL of *n*-BuLi solution (2.32 M in hexanes, 5.3 mmol) was added dropwise over 5 min. The resulting mixture was stirred at -78 °C for 30 min, and then ClCO₂Me (1.0 mL, 1.2 g, 13 mmol) was added in one portion. The reaction mixture was stirred at rt for 1 h, and then diluted with 30 mL of sat aq NaHCO₃ and 50 mL of ether. The aqueous phase was separated and extracted with two 30-mL portions of ether, and the combined organic phases were dried over MgSO₄, filtered, and concentrated to give 0.682 g of a dark-brown oil that was concentrated onto 2 g of silica gel which was added to the top of a column of 100 g of silica gel. Gradient elution with 0-10% EtOAc-hexanes furnished 0.444 g (68%) of **258** as a light-yellow viscous oil: IR (thin film) 2236, 1763, 1715, and 1554 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.24 (dd, *J* = 3.4, 1.7 Hz, 1 H), 6.47 (dd, *J* = 3.4, 1.7 Hz, 1 H), 6.16 (dd, *J* = 3.4, 3.4 Hz, 1 H), 3.98 (s, 3 H), 3.77 (s, 3 H), 2.63-2.55 (m, 4 H), and 1.90 (quint, *J* = 7.0 Hz, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 154.3, 150.5, 121.9, 120.2, 116.0, 111.7, 92.5, 89.0, 73.48, 73.46, 54.2, 52.8, 26.7, 19.1, and 17.9; HRMS (*m/z*) [M+Na⁺] calcd for C₁₅H₁₅NO₄ 296.0893; found, 296.0881.

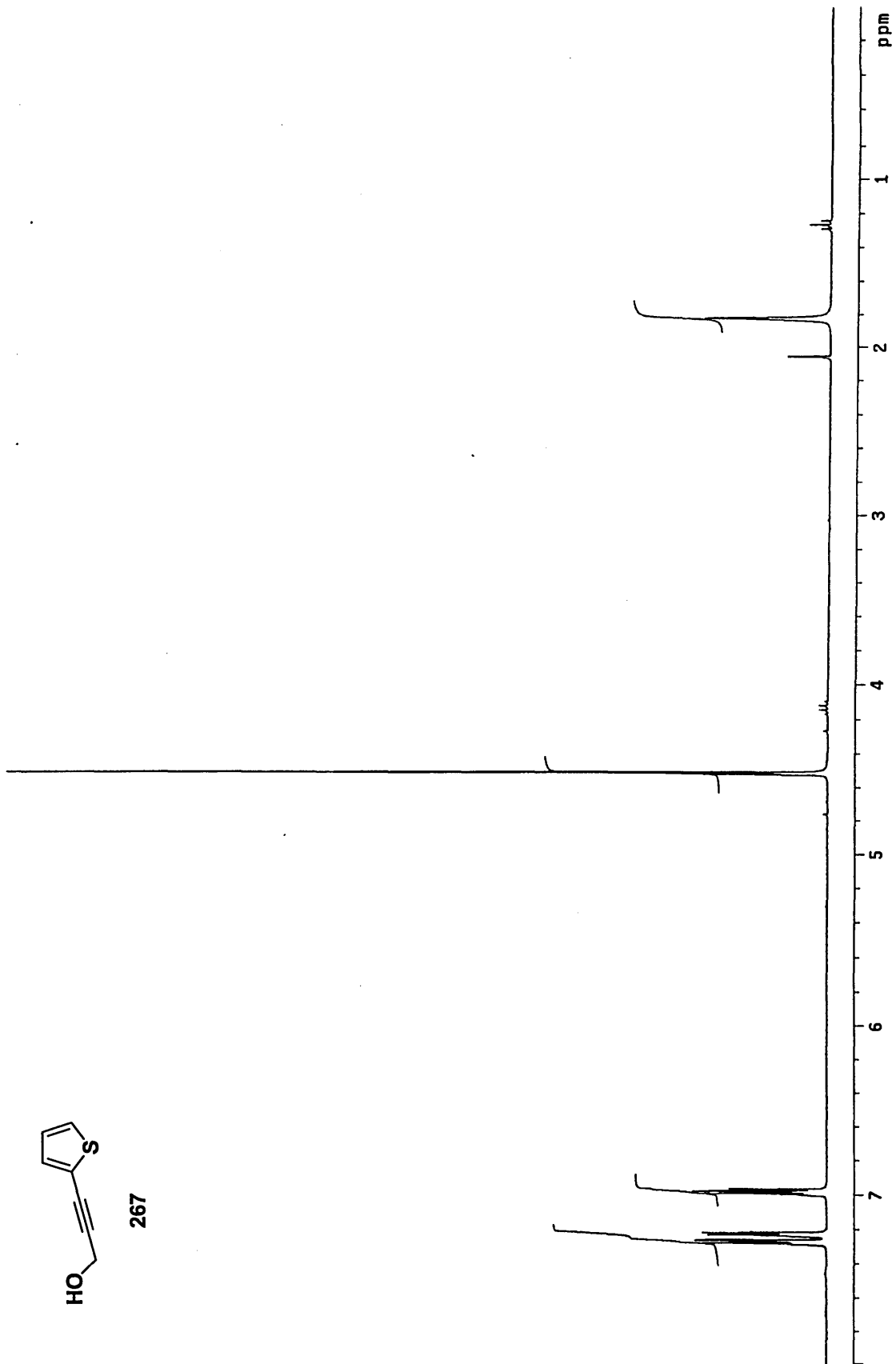


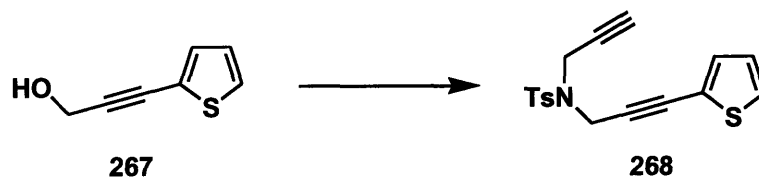


2-(3-Hydroxyprop-1-ynyl)thiophene (267). A 100-mL, three-necked, round-bottomed flask fitted with a glass stopper, rubber septum, and argon inlet adapter was charged with 2-iodothiophene (1.10 mL, 2.10 g, 10.0 mmol), 50 mL of THF, and piperidine (5.0 mL, 4.3 g, 50 mmol). Pd(PPh₃)₂Cl₂ (0.450 g, 0.641 mmol), CuI (0.230 g, 1.21 mmol), and propargyl alcohol (1.20 mL, 1.14 g, 20.3 mmol) were then added, and the resulting mixture was stirred for 2 h at rt and then filtered through 10 g of silica gel in a sintered glass funnel washing with 150 mL of diethyl ether. The filtrate was concentrated to yield 5 g of a dark-brown oil that was dissolved in 100 mL of CH₂Cl₂ and concentrated onto 10 g of silica gel which was added to the top of a column of 150 g of silica gel. Gradient elution with 0-20% EtOAc-hexanes afforded 1.370 g (99%) of **267** as a viscous dark-red oil: IR (thin film) 3322, 2223 and 1518 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.30 (dd, *J* = 5.0, 1.1 Hz, 1 H), 7.22 (dd, *J* = 3.6, 1.1 Hz, 1 H), 6.96 (dd, *J* = 5.0, 3.6 Hz, 1 H), 4.51 (d, *J* = 5.3 Hz, 2 H), and 3.03 (t, *J* = 5.3 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 132.4, 127.4, 127.0, 122.4, 91.3, 79.0, and 51.6; HRMS (*m/z*): [M⁺] calcd for C₇H₆OS 138.0134; found, 138.0134.

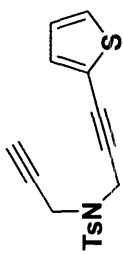


267

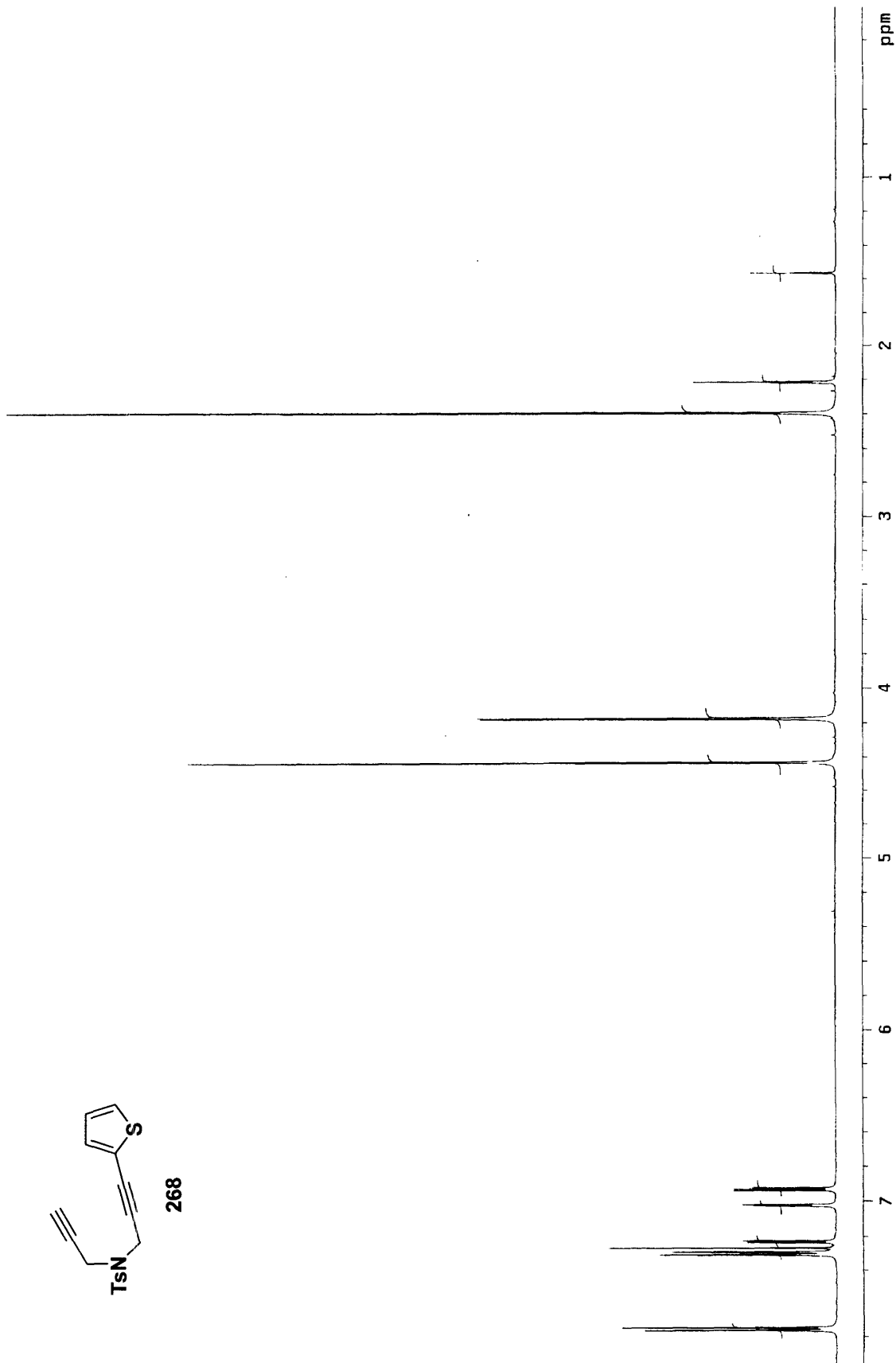


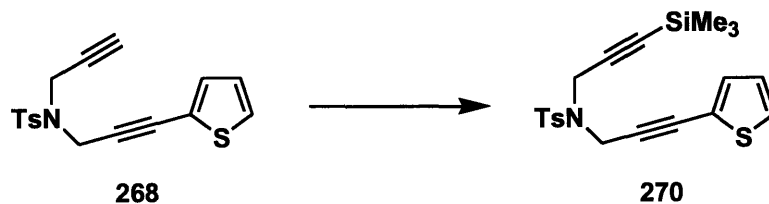


2-(3-[[4-Methylphenyl)sulfonyl]prop-2-ynylamino}prop-1-ynyl)thiophene (268). A 50-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of the alcohol **267** (0.909 g, 6.58 mmol) in 30 mL of THF, triphenylphosphine (1.898 g, 7.235 mmol), sulfonamide **229** (1.376 g, 6.534 mmol) and diisopropyl azodicarboxylate (1.42 mL, 1.46 g, 7.21 mmol). The reaction mixture was stirred at rt for 3 h and then concentrated under reduced pressure to furnish 6.321 g of a brown semisolid. This material was dissolved in 150 mL of CH_2Cl_2 and concentrated onto 15 g of silica gel which was added to the top of a column of 300 g of silica gel. Gradient elution with 0-10% EtOAc-hexanes provided 1.863 g (86%) of **268** an off-white solid: mp 81-82 °C; IR (thin film) 3107, 2224, 1597 and 1349 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.74 (d, $J = 8.2$ Hz, 2 H), 7.29 (d, $J = 8.3$ Hz, 2 H), 7.22 (dd, $J = 5.2, 1.1$ Hz, 1 H), 7.01 (dd, $J = 3.6, 1.1$ Hz, 1 H), 6.93 (dd, $J = 5.2, 3.6$ Hz, 1 H), 4.44 (s, 2 H), 4.18 (d, $J = 2.5$ Hz, 2 H), 2.40 (s, 3 H), and 2.24 (t, $J = 2.5$ Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.2, 135.1, 132.6, 129.8, 127.9, 127.6, 127.0, 122.0, 85.3, 79.3, 76.5, 74.3, 37.4, 36.7 and 21.7; HRMS (m/z): $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2\text{S}$ 3532.0436; found, 352.0435.

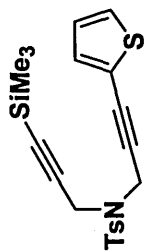


268

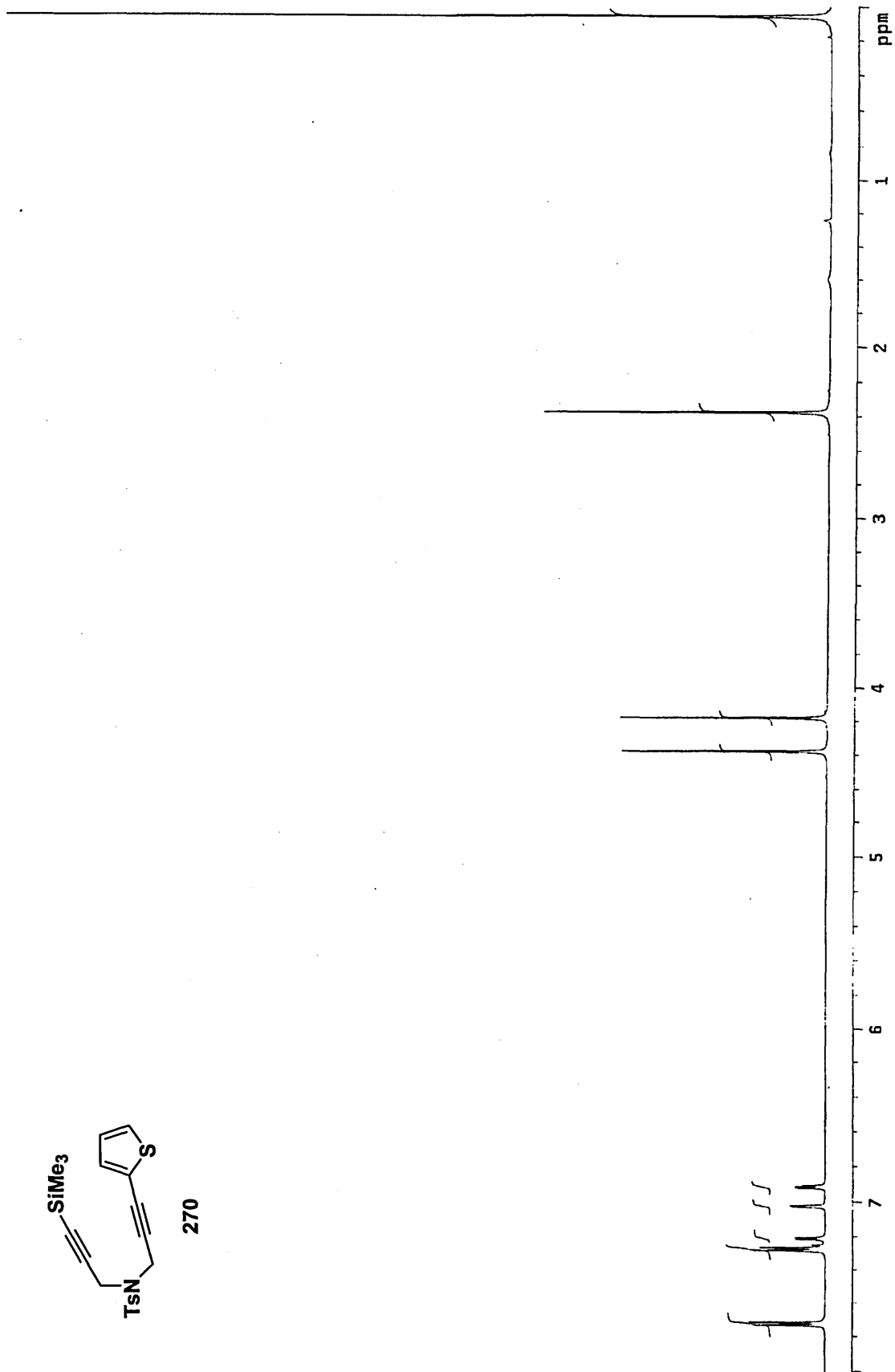


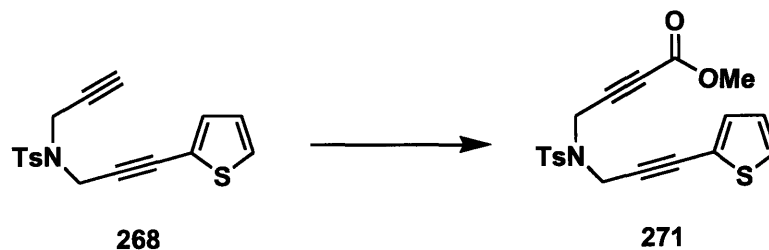


2-(3-((3-Trimethylsilyl)prop-2-ynyl)[(4-methylphenyl)sulfonyl]amino}prop-1-ynyl)thiophene (270). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with the the alkyne **268** (0.552 g, 1.34 mmol) and 4 mL of THF. The resulting solution was cooled to 0 °C and 0.21 mL of EtMgBr solution (2.95 M in diethyl ether, 0.60 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 0 °C for 30 min, and freshly distilled chlorotrimethylsilane (0.084 mL, 0.073 g, 0.67 mmol) was added dropwise over 1 min. The reaction mixture was allowed to warm to rt, stirred for 16 h, and then diluted with 10 mL of saturated aq NH₄Cl solution and 5 mL of Et₂O. The aqueous phase was separated and extracted with two 5-mL portions of Et₂O, and the combined organic phases were washed with 10 mL of saturated aq NaHCO₃ solution, 10 mL of 10% HCl solution, and 10 mL of brine, dried over MgSO₄, filtered, and concentrated to furnish 0.235 g of a light brown solid. This material was dissolved in 10 mL of CH₂Cl₂ and concentrated onto 1 g of silica gel which was added to the top of a column of 20 g of silica gel. Gradient elution with 0-1% EtOAc-hexanes provided 0.198 g (81%) of **270** as an off-white solid: mp 93-94 °C; IR (KBr) 2228, 2176, 1599, and 1344 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.23 (dd, *J* = 5.2, 0.8 Hz, 1 H), 7.04 (dd, *J* = 3.7, 0.8 Hz, 1 H), 6.94 (dd, *J* = 5.2, 3.7 Hz, 1 H), 4.40 (s, 2 H), 4.20 (s, 2 H), 2.40 (s, 3 H), and 0.08 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 143.9, 135.2, 132.5, 129.7, 127.9, 127.4, 126.9, 122.1, 97.7, 91.4, 85.7, 79.0, 37.8, 37.6, 21.9, and 0.0; HRMS (*m/z*): [M+Na⁺] calcd for C₂₀H₂₃NO₂S₂Si 424.0832; found, 424.0825.

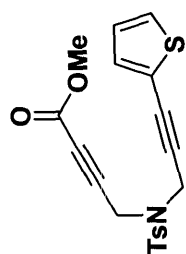


270

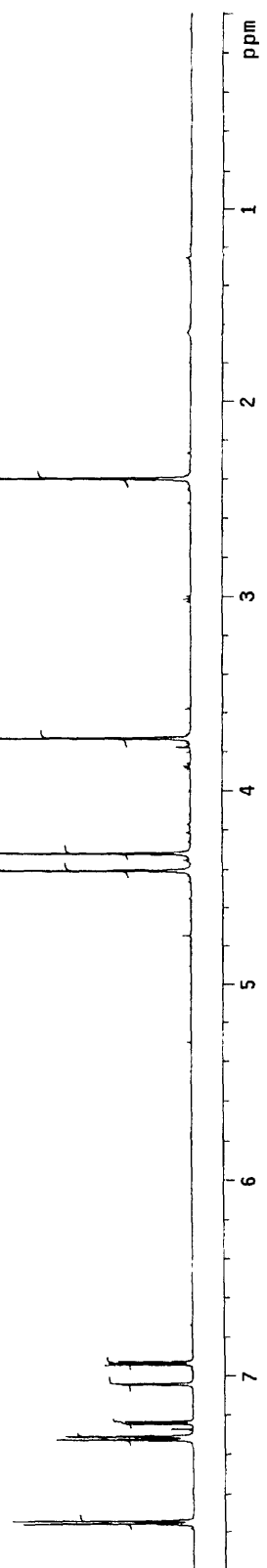


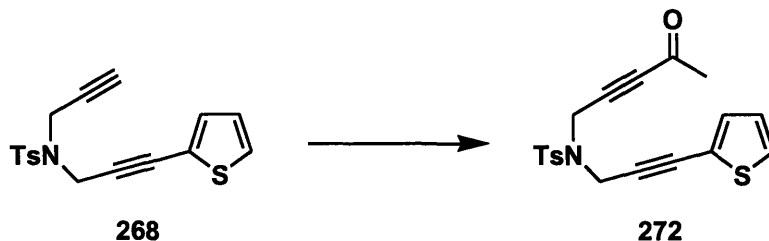


2-(3-((3-Methoxycarbonylbut-2-ynyl)[(4-methylphenyl)sulfonyl]amino)prop-1-ynyl)thiophene (**271**). A 50-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of the alkyne **268** (1.863 g, 5.656 mmol) in 30 mL of THF. The solution was cooled to 0 °C and 3.4 mL of EtMgCl solution (2.0 M in THF, 6.8 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 0 °C for 30 min, and methyl chloroformate (2.2 mL, 2.7 g, 28 mmol) was then added rapidly by syringe. The reaction mixture was allowed to warm to rt, stirred for 19 h, and then diluted with 20 mL of saturated aq NH₄Cl solution and 50 mL of Et₂O. The aqueous phase was separated and extracted with two 20-mL portions of Et₂O, and the combined organic phases were washed 30 mL of brine, dried over MgSO₄, filtered, and concentrated to furnish 2.314 g of a brown semisolid. This material was dissolved in 100 mL of CH₂Cl₂ and concentrated onto 6 g of silica gel which was added to the top of a column of 150 g of silica gel. Gradient elution with 0-10% EtOAc-hexanes provided 1.898 g (87%) of **271** as a brown viscous oil: IR (thin film) 2243, 1718, 1598, and 1353 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.74 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 7.23 (dd, *J* = 5.2, 1.2 Hz, 1 H), 7.04 (dd, *J* = 3.7, 1.2 Hz, 1 H), 6.93 (dd, *J* = 5.2, 3.7 Hz, 1 H), 4.40 (s, 2 H), 4.32 (s, 2 H), 3.73 (s, 3 H) and 2.40 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 153.2, 144.5, 134.8, 132.9, 130.0, 128.0, 127.8, 127.0, 121.8, 84.9, 80.5, 79.8, 77.2, 52.9, 38.0, 36.8, and 21.7; HRMS (*m/z*): [M+Na⁺] calcd for C₁₉H₁₇NO₄S₂ 410.0491; found, 410.0503.

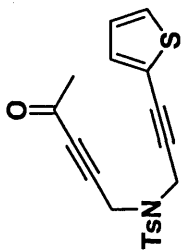


271

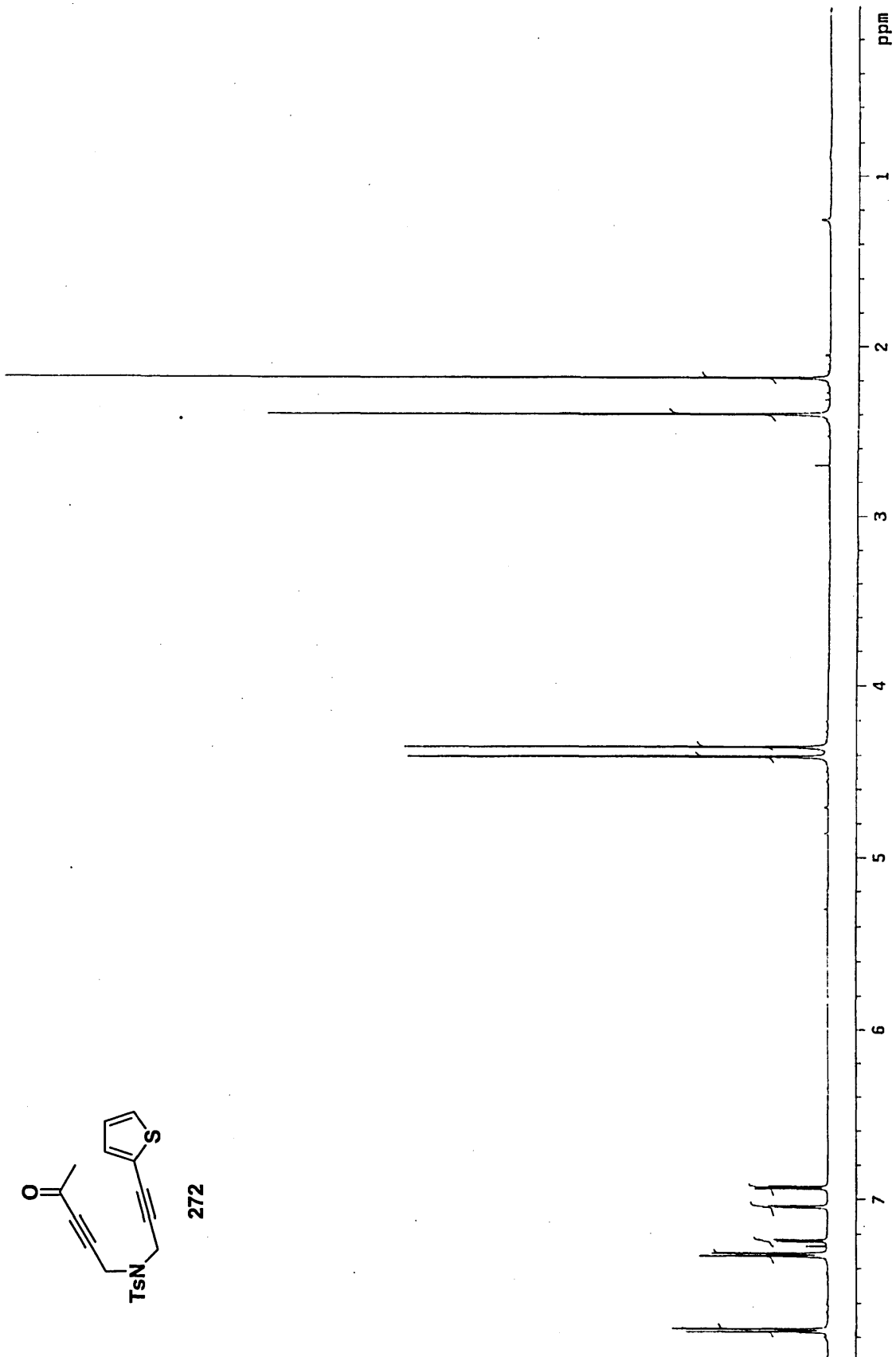


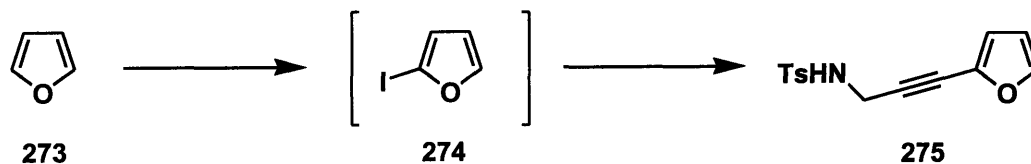


2-(3-((4-Oxopent-2-ynyl)[(4-methylphenyl)sulfonyl]amino)prop-1-ynyl)thiophene (272). A 50-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with the alkyne **268** (0.318 g, 0.967 mmol) and 10 mL of THF. The solution was cooled to 0 °C and 0.45 mL of EtMgBr solution (3.0 M in diethyl ether, 1.2 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 0 °C for 30 min, and freshly distilled acetaldehyde (0.30 mL, 0.23 g, 5.3 mmol) was then added in one portion. The reaction mixture was stirred for 1 h at 0 °C, 2 h at rt, and then diluted with 10 mL of saturated aq NH₄Cl solution and 20 mL of Et₂O. The aqueous phase was separated and extracted with two 10-mL portions of Et₂O, and the combined organic phases were washed with 20 mL of brine, dried over MgSO₄, filtered, and concentrated to furnish 0.397 g of a yellow oil. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 1 g of silica gel which was added to the top of a column of 10 g of silica gel. Elution with 5% EtOAc-hexanes provided 0.342 g of the corresponding secondary alcohol as a light yellow oil, which was dissolved in 10 mL of CH₂Cl₂ in a 50-mL round bottomed flask fitted with a rubber septum and an argon inlet needle. Dess-Martin periodinane (0.582 g, 1.37 mmol) was added, and the reaction mixture was stirred at rt for 2 h, then diluted with 20 mL of half-saturated aq NaHCO₃ solution and 20 mL of CH₂Cl₂. The aqueous phase was separated and extracted with two 20-mL portions of CH₂Cl₂, and the combined organic phases were then washed with 20 mL of half-saturated aq NaHCO₃ solution, 20 mL of brine, dried over MgSO₄, filtered, and concentrated to furnish 0.306 g of a light-brown oil that was concentrated onto 1 g of silica gel, which was added to the top of a column of 10 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes yielded 0.271 g (76% from **268**) of **272** as a light-brown oil: IR (thin film) 2217, 1680, 1597, and 1353 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.77 (d, *J* = 8.5 Hz, 2 H), 7.33 (d, *J* = 8.5 Hz, 2 H), 7.23 (dd, *J* = 5.2, 1.1 Hz, 1 H), 7.04 (dd, *J* = 3.7, 1.1 Hz, 1 H), 6.93 (dd, *J* = 5.2, 3.7 Hz, 1 H), 4.42 (s, 2 H), 4.36, (s, 2 H), 2.41 (s, 3 H), and 2.19 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 183.7, 143.6, 135.0, 132.9, 130.0, 128.1, 127.9, 127.1, 121.8, 85.0, 84.9, 84.2, 79.9, 38.2, 37.0, 32.6, and 21.8; HRMS (*m/z*) [M+Na⁺] calcd for C₁₉H₁₇NO₃S₂ 394.0542; found, 394.0532.



272

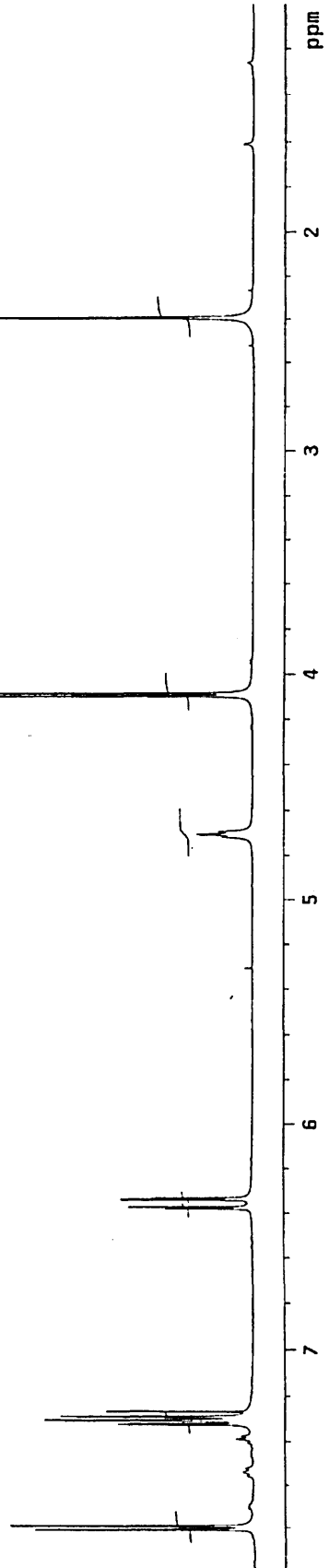


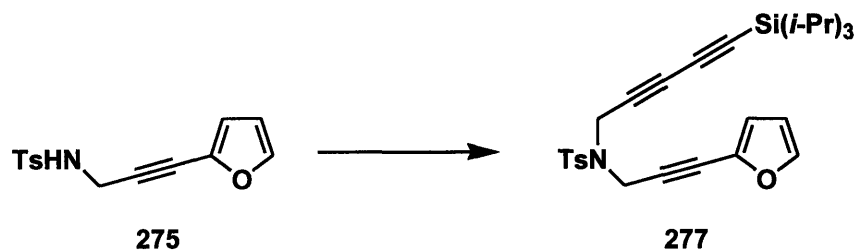


2-([3-{4-Methylphenylsulfonyl}amino]prop-2-ynyl)furan (275). A 100-mL, round-bottomed flask equipped with an addition funnel fitted with a rubber septum and argon inlet needle was charged with a solution of furan (1.00 mL, 0.936 g, 13.8 mmol) in 10 mL of ether and cooled to 0 °C. The addition funnel was charged with 10 mL of ether, TMEDA (2.5 mL, 1.9 g, 17 mmol) and *n*-BuLi solution (2.39 M in hexanes, 7.0 mL, 17 mmol), and this solution was added dropwise to the reaction mixture over 2 min, (5 mL ether rinse). The funnel was replaced with a rubber septum and argon inlet needle, and the reaction mixture was stirred at 0 °C for 30 min. A solution of I₂ (4.536 g, 17.9 mmol) in 40 mL of ether was then added via cannula over 5 min (5 mL ether rinse) and the resulting mixture was allowed to warm to rt, stirred for 18 h, and diluted with 20 mL of saturated Na₂S₂O₃ solution and 50 mL of ether. The organic phase was separated and washed with 50 mL of water, and the combined aqueous phases were extracted with two 50-mL portions of ether. The combined organic phases were washed with 50 mL of brine, dried over MgSO₄, filtered, and concentrated to give 1.356 g of dark-red oil that was immediately dissolved in 30 mL of THF in a 50-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle. Piperidine (3.5 mL, 3.0 g, 35 mmol), Pd(PPh₃)₂Cl₂ (0.245 g, 0.349 mmol), CuI (0.156 g, 0.819 mmol), and sulfonamide **229** (1.396 g, 6.671 mmol) were then added, and the resulting mixture was stirred at rt for 2 h. The reaction mixture was then filtered through 10 g of silica gel in a sintered glass funnel washing with 100 mL of ether and concentrated to give 2.561 g of a brown semi-solid. This material was dissolved in 50 mL of CH₂Cl₂ and concentrated onto 5 g of silica gel which was added to the top of a column of 150 g of silica gel. Gradient elution with 0-25% EtOAc-hexanes furnished 0.523 g (28%, two steps) of the sulfonamide **275** as a light-brown solid: mp 140-142 °C; IR (film) 3267, 2242, 1597, 1572, and 1318 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, *J* = 8.4 Hz, 2 H), 7.32 (dd, *J* = 1.8, 0.8 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 6.38 (dd, *J* = 3.3, 0.8 Hz, 1 H), 6.34 (dd, *J* = 3.3, 1.8 Hz, 1 H), 4.71 (t, *J* = 6.2 Hz, 1 H), 4.09, (d, *J* = 6.2 Hz, 2 H), and 2.40 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 144.1, 143.9, 136.7, 136.2, 129.9, 127.7, 115.9, 111.0, 87.9, 75.3, 34.0, and 21.8; HRMS (*m/z*): [M+Na⁺] calcd for C₁₄H₁₃NO₃S 298.0508; found, 298.0507.

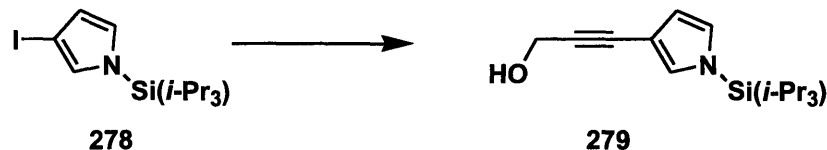


275





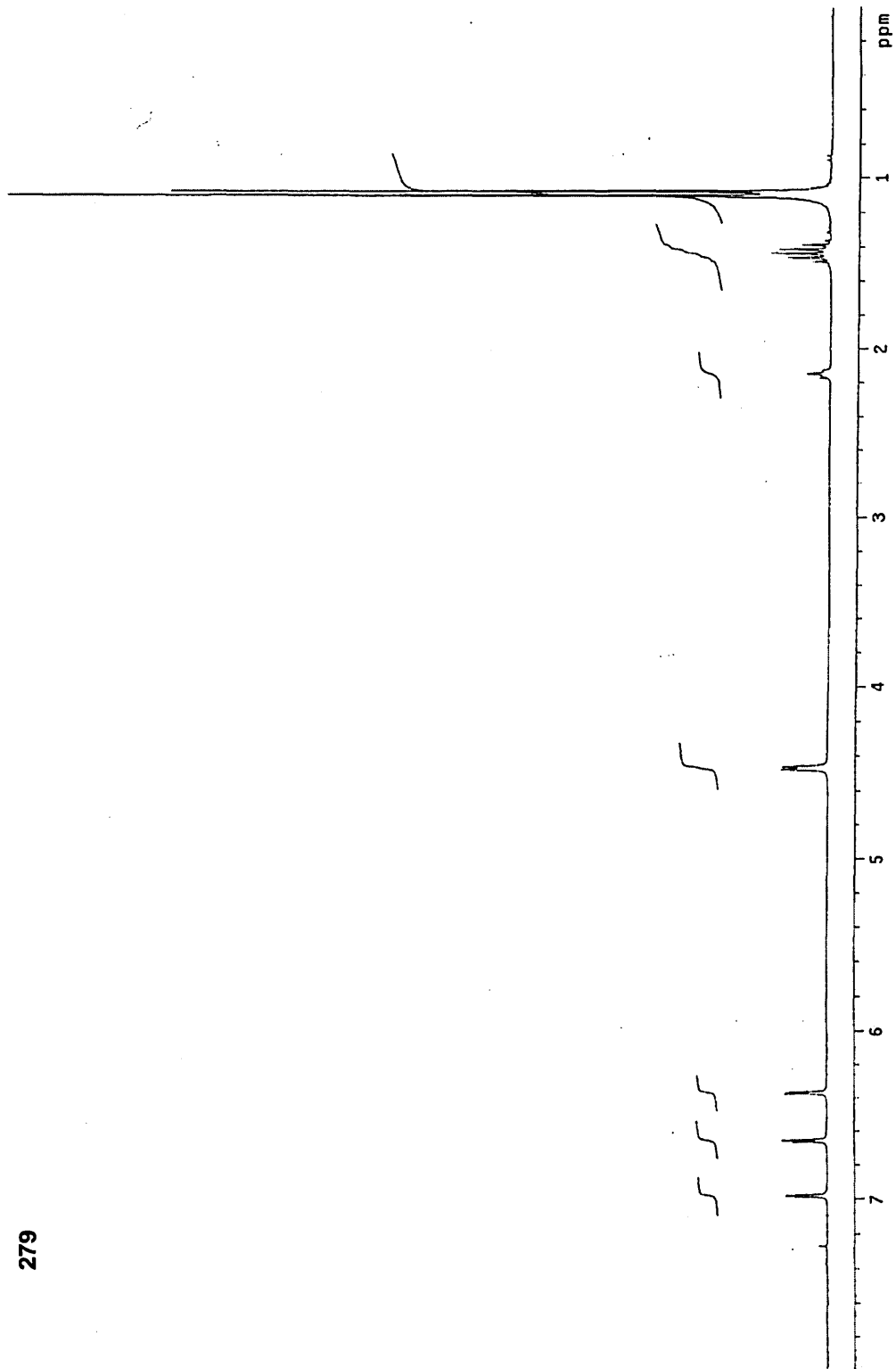
2-(3-{{(4-Methylphenyl)sulfonyl]-5-(triisopropylsilyl)penta-2,4-diyne}}prop-1-ynyl)furan (277). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of the sulfonamide **277** (0.434 g, 1.57 mmol) in 8 mL of THF, triphenylphosphine (0.496 g, 1.89 mmol), alcohol **231** (0.410 g, 1.73 mmol), and diisopropyl azodicarboxylate (0.37 mL, 0.38 g, 1.9 mmol). The reaction mixture was stirred at rt for 3 h and then concentrated under reduced pressure to furnish 1.978 g of a brown semisolid. This material was dissolved in 50 mL of CH_2Cl_2 and concentrated onto 5 g of silica gel which was added to the top of a column of 150 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes provided 0.530 g (68%) of **277** as a viscous red oil: IR (thin film) 2224, 2107, 1598, 1573, and 1355 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.75 (d, $J = 8.3$ Hz, 2 H), 7.33 (dd, $J = 1.9, 0.8$ Hz, 1 H), 7.30 (d, $J = 8.3$ Hz, 2 H), 6.44 (dd, $J = 3.3, 0.8$ Hz, 1 H), 6.34 (dd, $J = 3.3, 1.9$ Hz, 1 H), 4.38 (s, 2 H), 4.28 (s, 2 H), 2.38 (s, 3 H), and 1.18-1.00 (m, 21 H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.3, 143.9, 136.2, 134.9, 129.8, 128.1, 116.1, 110.9, 88.8, 86.0, 84.2, 76.6, 71.2, 69.5, 37.8, 37.5, 21.7, 18.7 and 11.3; HRMS (m/z): $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{28}\text{H}_{35}\text{NO}_3\text{Si}$ 516.1999; found, 516.1971.

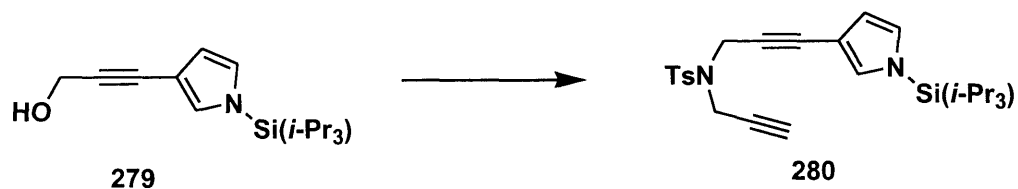


1-(Triisopropylsilyl)-3-(3-hydroxyprop-1-ynyl)pyrrole (279). A 50-mL, round-bottomed flask fitted with an argon inlet adapter was charged with 3-iodopyrrole **278** (1.138 g, 3.257 mmol), 15 mL of THF, and piperidine (1.6 mL, 1.4 g, 16 mmol). Pd(PPh₃)₂Cl₂ (0.136 g, 0.194 mmol), CuI (0.094 g, 0.49 mmol), and propargyl alcohol (0.38 mL, 0.36 g, 6.4 mmol) were then added, and the resulting mixture was stirred for 2 h at rt and then filtered through 7 g of silica gel with the aid of 50 mL of diethyl ether. The filtrate was concentrated under reduced pressure to yield 1.871 g of a dark red semisolid that was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 5 g of silica gel which was added to the top of a column of 45 g of silica gel. Gradient elution with 5-10% EtOAc-hexanes afforded 0.593 g (66%) of **279** as a light-brown oil: ¹H NMR (300 MHz, CDCl₃) δ 6.98 (dd, *J* = 2.2, 1.6 Hz, 1 H), 6.66 (dd, *J* = 3.3, 2.2 Hz, 1 H), 6.37 (dd, *J* = 3.3, 1.6 Hz, 1 H), 4.47 (d, *J* = 5.0 Hz, 2 H), 2.15 (t, *J* = 5.0 Hz, 1 H), 1.44 (sept, *J* = 7.5 Hz, 3 H), and 1.10 (d, *J* = 7.5 Hz, 18 H); ¹³C NMR (75 MHz, CDCl₃) δ 128.7, 124.2, 113.7, 105.5, 86.2, 81.7, 52.0, 17.9, and 11.8.

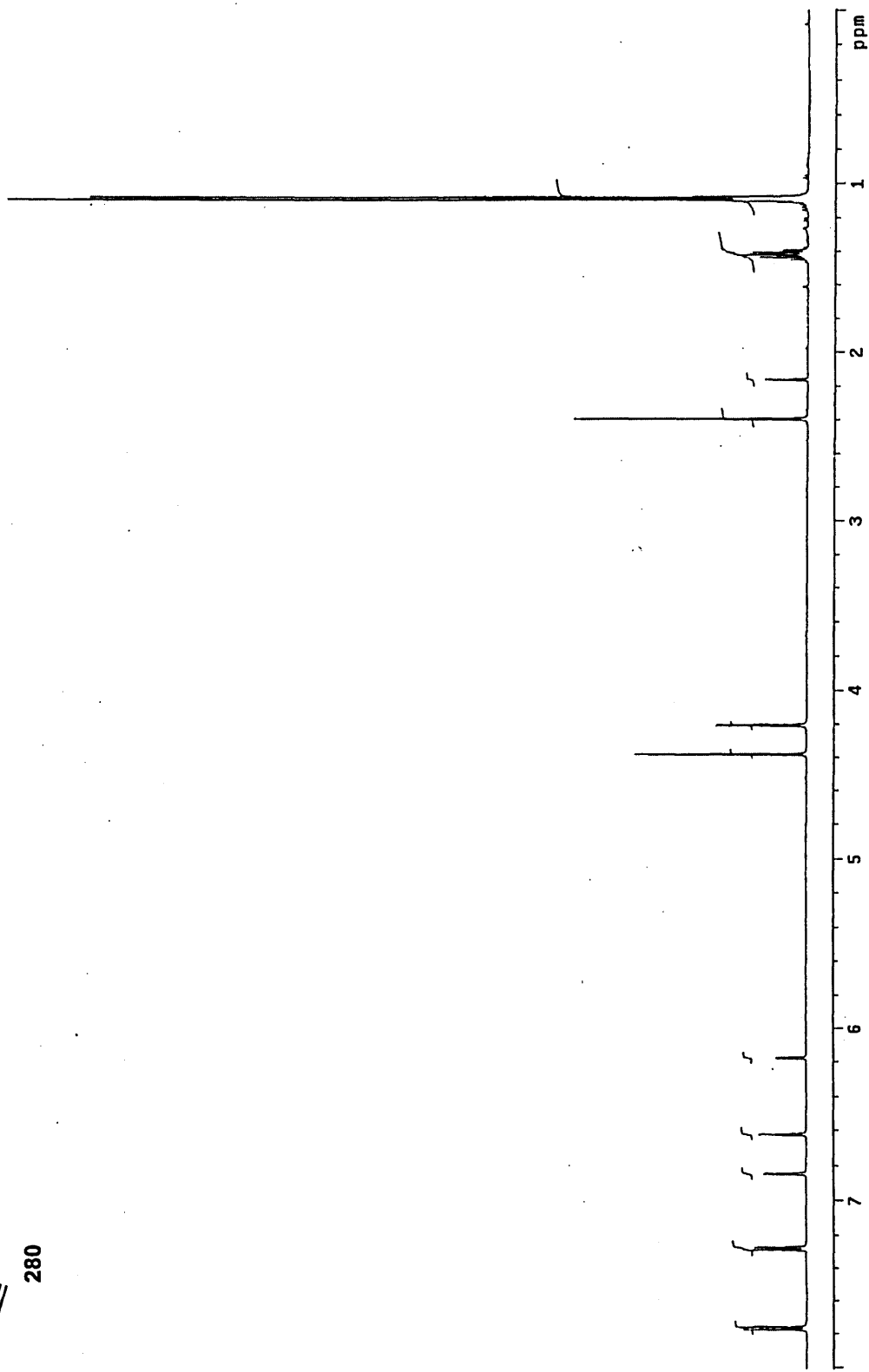
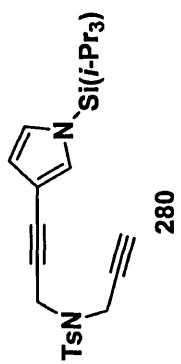


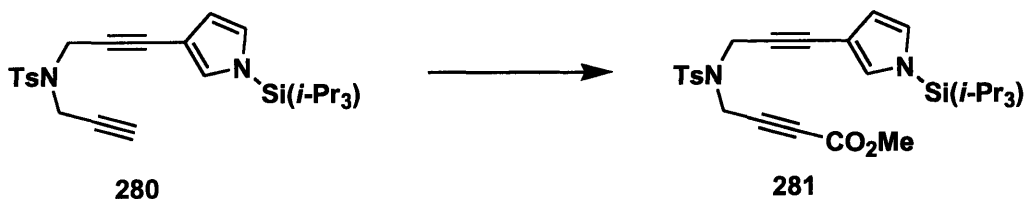
279



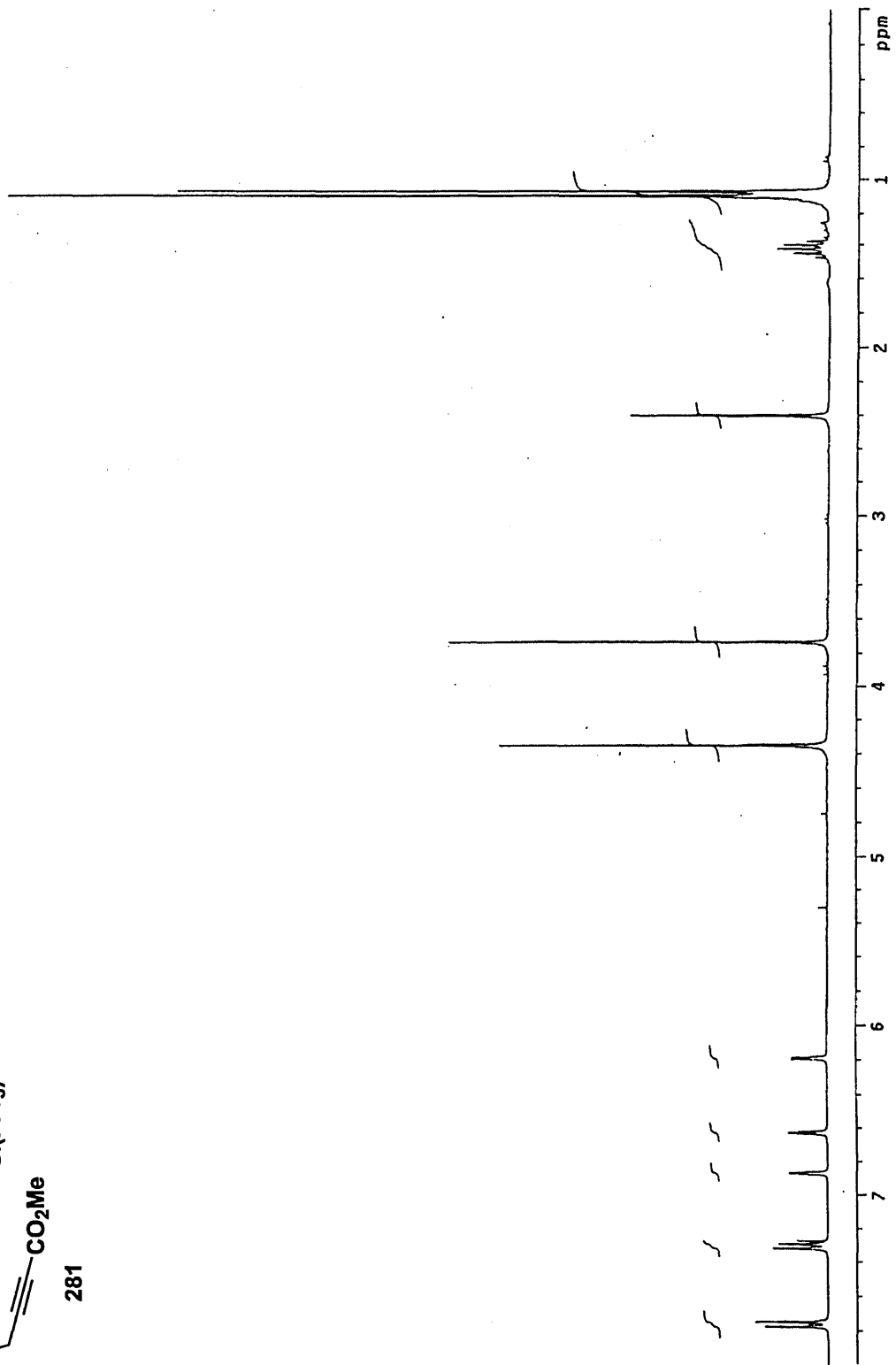
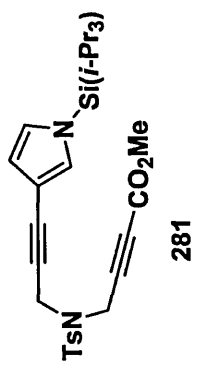


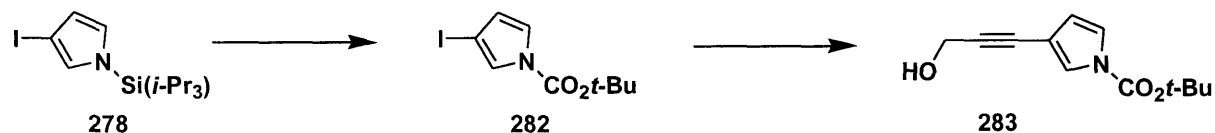
1-(Triisopropylsilyl)-3-(3-((4-methylphenyl)sulfonyl)prop-2-ynylamino)-prop-1-ynyl-pyrrole (280). A 50-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with the alcohol **279** (0.580 g, 2.09 mmol), 10 mL of THF, sulfonamide **229** (0.481 g, 2.30 mmol) and triphenylphosphine (0.658 g, 2.51 mmol). Diethyl azodicarboxylate (0.40 mL, 0.45 g, 2.5 mmol) was added dropwise via syringe over 1 min, and the reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure to furnish 2.366 g of a brown semisolid. This material was dissolved in 50 mL of CH₂Cl₂ and concentrated onto 5 g of silica gel which was added to the top of a column of 50 g of silica gel. Gradient elution with 2-5% EtOAc-hexanes provided 0.819 g (87%) of **280** as light-yellow paste: ¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, *J* = 8.0 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 6.84 (dd, *J* = 2.2, 1.6 Hz, 1 H), 6.62 (dd, *J* = 3.3, 2.2 Hz, 1 H), 6.17 (dd, *J* = 3.3, 1.6 Hz, 1 H), 4.39 (s, 2 H), 4.21 (d, *J* = 2.2 Hz, 2 H), 2.40 (s, 3 H), 2.18 (t, *J* = 2.2 Hz, 1 H), 1.43 (sept, *J* = 7.4 Hz, 3 H), and 1.10 (d, *J* = 7.4 Hz, 18 H); ¹³C NMR (75 MHz, CDCl₃) δ 143.6, 135.3, 129.5, 128.5, 127.9, 124.0, 113.7, 105.2, 81.8, 79.8, 76.8, 73.9, 37.6, 36.4, 21.8, 17.9, and 11.7.





1-(Triisopropylsilyl)-3-(3-((3-methoxycarbonylprop-2-ynyl)[(4-methylphenyl)sulfonyl]-amino)prop-1-ynyl)pyrrole (281). A 50-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of the alkyne **280** (0.983 g, 2.10 mmol) in 10 mL of THF. The solution was cooled to 0 °C and 0.79 mL of EtMgBr solution (2.95 M in diethyl ether, 2.3 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 0 °C for 30 min, and methyl chloroformate (0.80 mL, 0.98 g, 10 mmol) was then added rapidly by syringe. The reaction mixture was allowed to warm to rt, stirred for 21 h, and then diluted with 10 mL of saturated aq NH₄Cl solution and 30 mL of Et₂O. The aqueous phase was separated and extracted with two 20-mL portions of Et₂O, and the combined organic phases were washed with 25 mL of brine, dried over MgSO₄, filtered, and concentrated to furnish 1.108 g of a light-brown semisolid. This material was dissolved in 50 mL of CH₂Cl₂ and concentrated onto 2 g of silica gel which was added to the top of a column of 20 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes provided 0.840 g (76%) of **281** as light-yellow gum: IR (thin film) 2237, 1720, 1598, and 1163 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 6.86 (dd, *J* = 2.2, 1.6 Hz, 1 H), 6.62 (dd, *J* = 3.3, 2.2 Hz, 1 H), 6.18 (dd, *J* = 3.3, 1.6 Hz, 1 H), 4.35 (s, 4 H), 3.73 (s, 3 H), 2.40 (s, 3 H), 1.42 (sept, *J* = 7.4 Hz, 3 H), and 1.09 (d, *J* = 7.4 Hz, 18 H); ¹³C NMR (75 MHz, CDCl₃) δ 153.3, 148.1, 144.2, 135.1, 130.0, 129.0, 128.1, 124.3, 113.9, 105.2, 82.6, 81.0, 79.5, 77.0, 52.9, 38.2, 36.4, 21.7, 17.9, and 11.7.

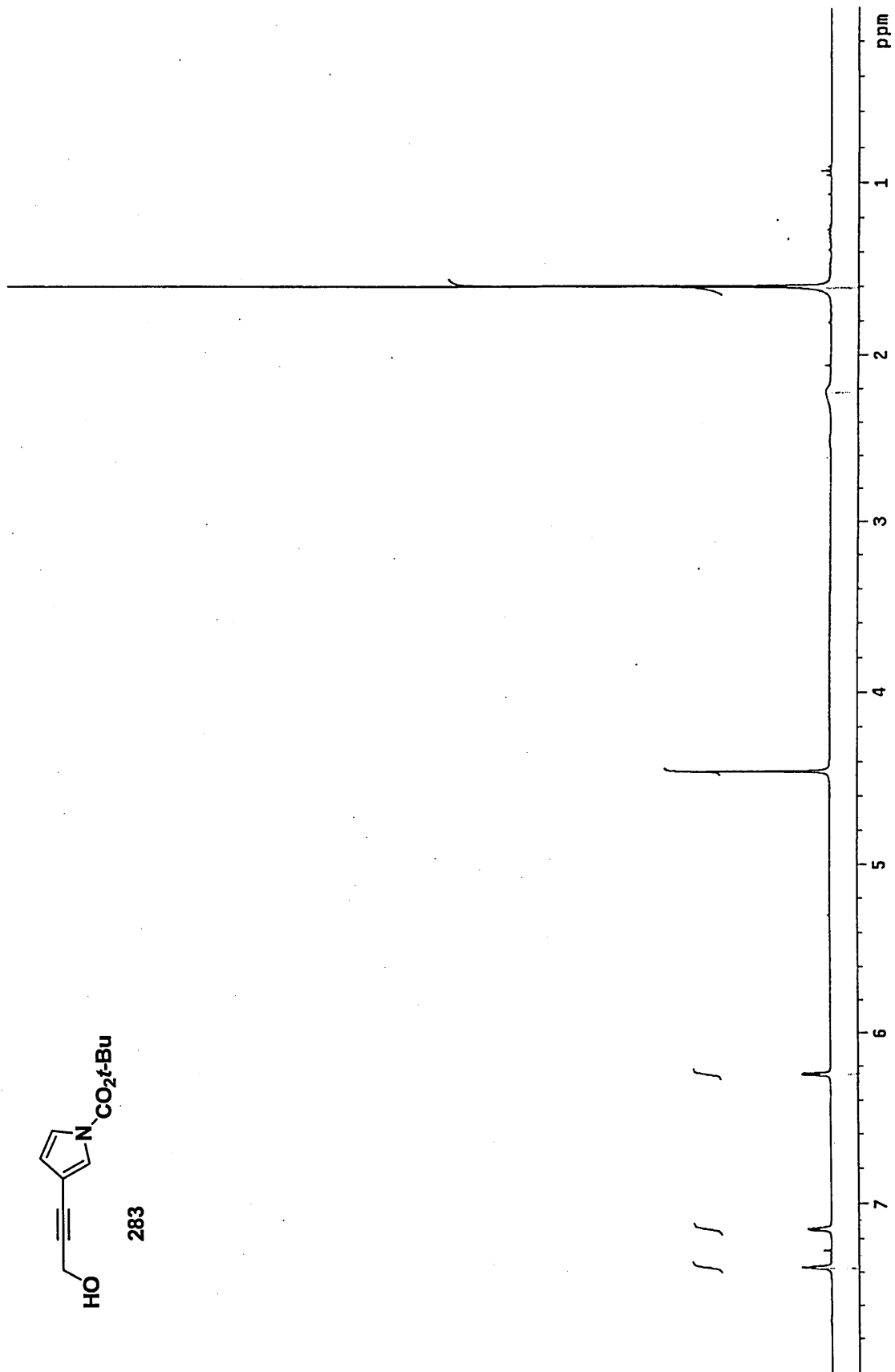


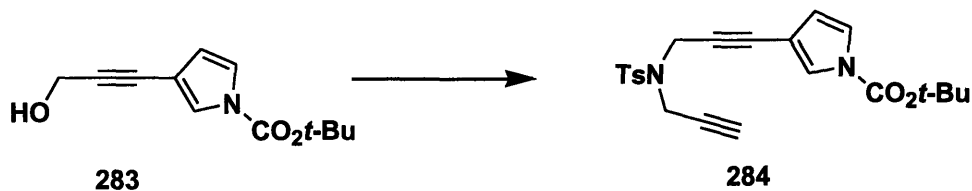


1-(*t*-Butoxycarbonyl)-3-(3-hydroxyprop-1-ynyl)pyrrole (283). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the iodopyrrole **278** (1.602 g, 4.585 mmol), 10 mL of THF and 4.6 mL of TBAF solution (1.0 M in THF, 4.6 mmol). The resulting mixture was stirred at rt for 15 min, concentrated under reduced pressure, and then diluted with 30 mL of water and 30 mL of hexanes. The phases were separated and the organic phase was washed with two 20-mL portions of water, one 20-mL of brine, then dried over dried over MgSO_4 , filtered, and concentrated under reduced pressure in a 50-mL, round-bottomed flask, to which were immediately added 15 mL of THF, triethylamine (0.64 mL, 0.46 g, 4.6 mmol), DMAP (0.056 g, 0.46 mmol), and di-*t*-butyl-dicarbonate (1.200 g, 5.499 mmol). The resulting mixture was stirred at rt for 2 h, then diluted with 30 mL of water and 30 mL of hexanes. The phases were separated and the organic phase was washed with two 20-mL portions of water, one 20-mL portion of brine, then dried over MgSO_4 , filtered and concentrated to furnish 2.556 g of a light-brown oil that was added to the top of a column of 50 g of silica gel which had been pre-treated with a solution of 5% triethylamine-hexanes. Elution with pure hexanes and concentration of column fractions furnished 2.084 g of impure pyrrole **282** as a light-brown oil that was dissolved in 30 mL of THF in a 50-mL, round-bottomed flask. To this solution were added piperidine (2.3 mL, 2.0 g, 23 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.195 g, 0.278 mmol), CuI (0.106 g, 0.557 mmol), and propargyl alcohol (0.54 mL, 0.51 g, 9.1 mmol), and the resulting mixture was stirred for 2 h at rt and then filtered through 5 g of silica gel in a sintered glass funnel washing with 100 mL of diethyl ether. The filtrate was concentrated under reduced pressure to yield 4.390 g of a dark red semisolid that was dissolved in 50 mL of CH_2Cl_2 and concentrated onto 10 g of silica gel which was added to the top of a column of 100 g of silica gel. Gradient elution with 0-20% EtOAc-hexanes afforded 0.899 g (87%, three steps) of **283** as a viscous light red oil: IR (thin film) 3375, 2231, 1747, and 1560 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.37 (dd, $J = 2.2, 1.6$ Hz, 1 H), 7.15 (dd, $J = 3.3, 2.2$ Hz, 1 H), 6.25 (dd, $J = 3.3, 1.6$ Hz, 1 H), 4.47 (s, 2 H), 2.22 (s, 1 H), 1.61 (s, 9 H); ^{13}C NMR (75 MHz, CDCl_3) δ 148.1, 123.7, 120.1, 114.7, 107.6, 87.5, 84.6, 79.8, 51.8, and 28.2; HRMS (m/z): $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_3$ 244.0944; found, 244.0950.

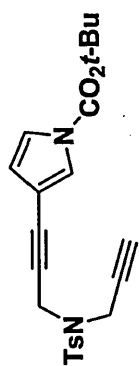


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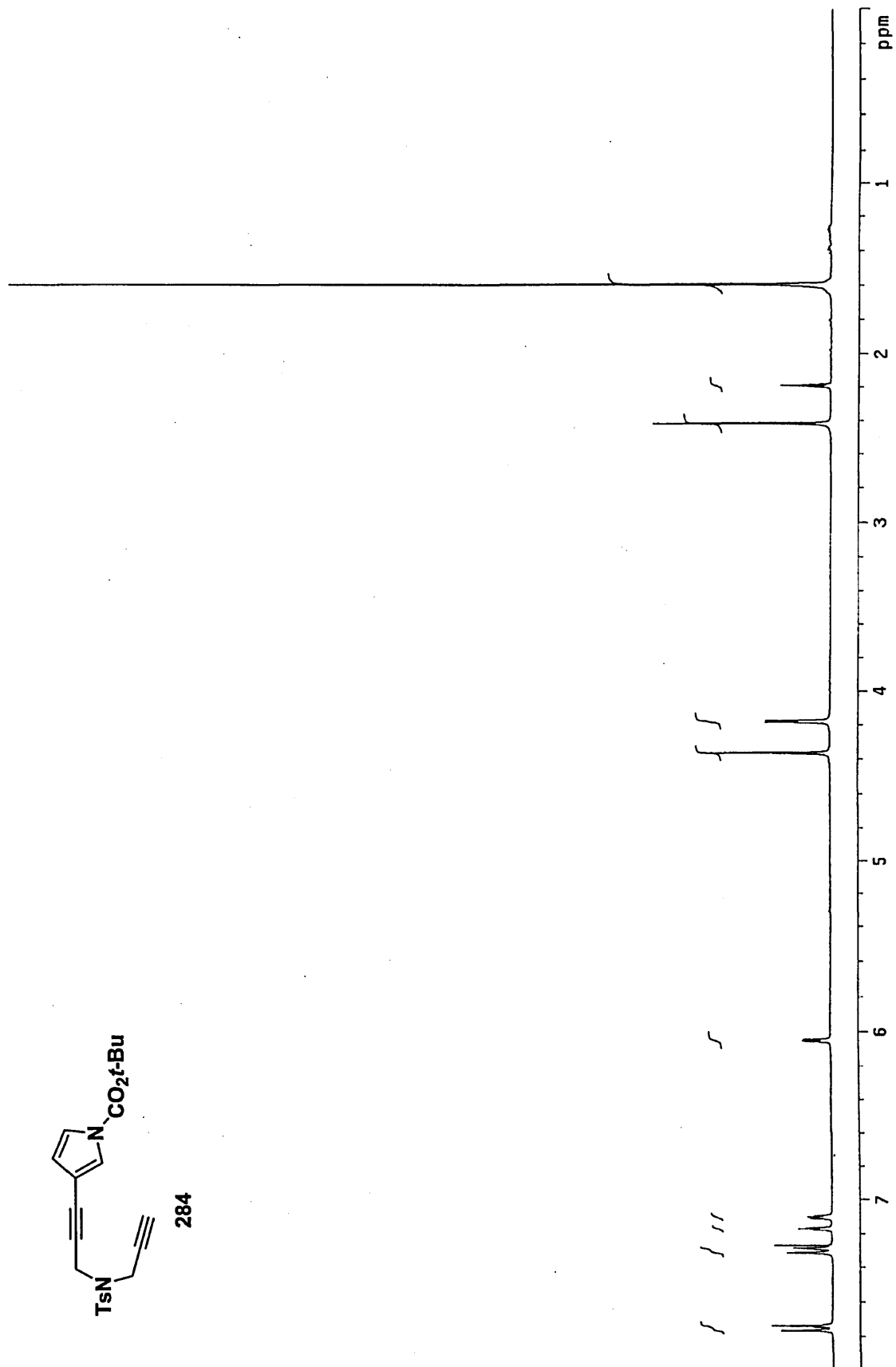


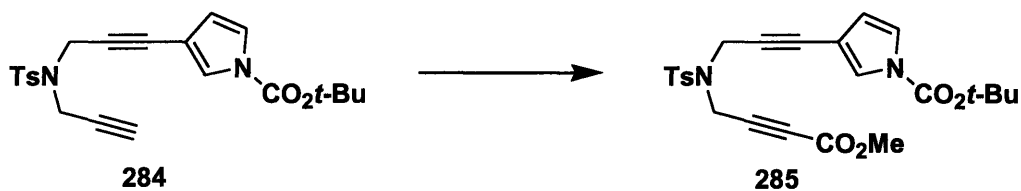


1-(*t*-Butoxycarbonyl)-3-(3-[[4-methylphenyl)sulfonyl]prop-2-ynylamino}prop-1-ynyl)-pyrrole (284). A 50-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with the alcohol **283** (0.824 g, 3.72 mmol), 20 mL of THF, the sulfonamide **229** (0.856 g, 4.09 mmol) and triphenylphosphine (1.172 g, 4.466 mmol). Diisopropyl azodicarboxylate (0.90 mL, 0.92 g, 4.6 mmol) was added dropwise via syringe over 1 min, and the reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure to furnish 3.980 g of a brown semisolid. This material was dissolved in 100 mL of CH₂Cl₂ and concentrated onto 10 g of silica gel which was added to the top of a column of 150 g of silica gel. Gradient elution with 0-10% EtOAc-hexanes provided 1.339 g (87%) of **284** as an off-white solid: mp 99-101 °C; IR (thin film) 3288, 2235, 2125, 1742, 1598, and 1384 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.17 (dd, *J* = 2.2, 1.6 Hz, 1 H), 7.11 (dd, *J* = 3.3, 2.2 Hz, 1 H), 6.05 (dd, *J* = 3.3, 1.6 Hz, 1 H), 4.37 (s, 2 H), 4.17 (d, *J* = 2.5 Hz, 2 H), 2.42 (s, 3 H), 2.19 (t, *J* = 2.5 Hz, 1 H), and 1.60 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 148.1, 144.0, 135.5, 129.7, 128.1, 123.9, 120.1, 114.6, 107.2, 84.7, 81.4, 81.1, 76.7, 74.1, 37.4, 36.6, 28.1, and 21.7; HRMS (*m/z*): [M+Na⁺] calcd for C₂₂H₂₄N₂O₄S 435.1349; found, 435.1357.

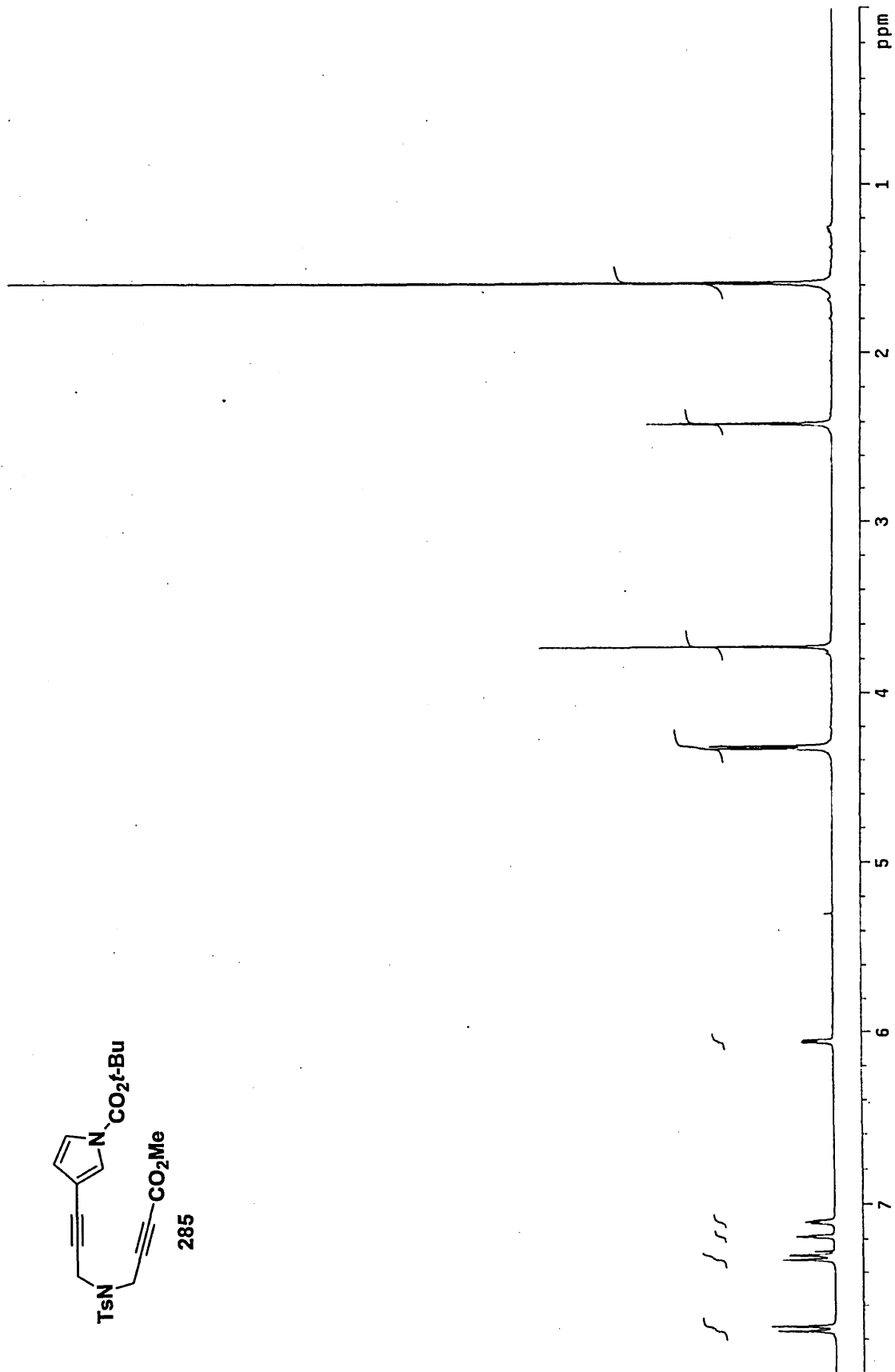
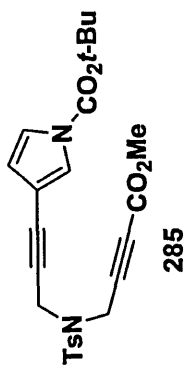


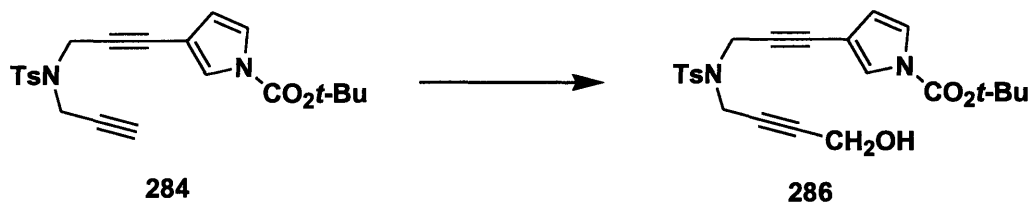
284



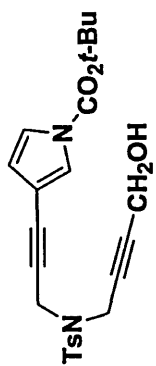


1-(*t*-Butoxycarbonyl)-3-(3-((3-methoxycarbonylprop-2-ynyl)[(4-methylphenyl)sulfonyl]-amino}prop-1-ynyl)pyrrole (285). A 50-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of the alkyne **284** (0.552 g, 1.34 mmol) in 6 mL of THF. The solution was cooled to 0 °C and 0.50 mL of EtMgBr solution (2.95 M in diethyl ether, 1.5 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 0 °C for 30 min, and methyl chloroformate (0.52 mL, 0.64 g, 6.7 mmol) was then added rapidly by syringe. The reaction mixture was allowed to warm to rt, stirred for 17 h, and then diluted with 10 mL of saturated aq NH₄Cl solution and 20 mL of Et₂O. The aqueous phase was separated and extracted with two 10-mL portions of Et₂O, and the combined organic phases were washed with 25 mL of brine, dried over MgSO₄, filtered, and concentrated to furnish 0.653 g of a brown semisolid. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 2 g of silica gel which was added to the top of a column of 20 g of silica gel. Gradient elution with 0-10% EtOAc-hexanes provided 0.492 g (78%) of **285** as an off-white solid: mp 109-110 °C; IR (thin film) 2241, 1748, 1720, 1598, and 1385 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.74 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 7.18 (dd, *J* = 2.2, 1.6 Hz, 1 H), 7.10 (dd, *J* = 3.3, 2.2 Hz, 1 H), 6.06 (dd, *J* = 3.3, 1.6 Hz, 1 H), 4.38-4.28 (m, 4 H), 3.73 (s, 3 H), 2.41 (s, 3 H), and 1.59 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 153.3, 148.1, 144.4, 135.0, 129.9, 128.1, 124.1, 120.1, 114.6, 107.0, 84.7, 80.9, 80.73, 80.67, 77.1, 53.0, 38.0, 36.6, 38.8, 36.6, 28.1, and 21.7; HRMS (*m/z*): [M+Na⁺] calcd for C₂₄H₂₆N₂O₆S 493.1404; found, 493.1415.

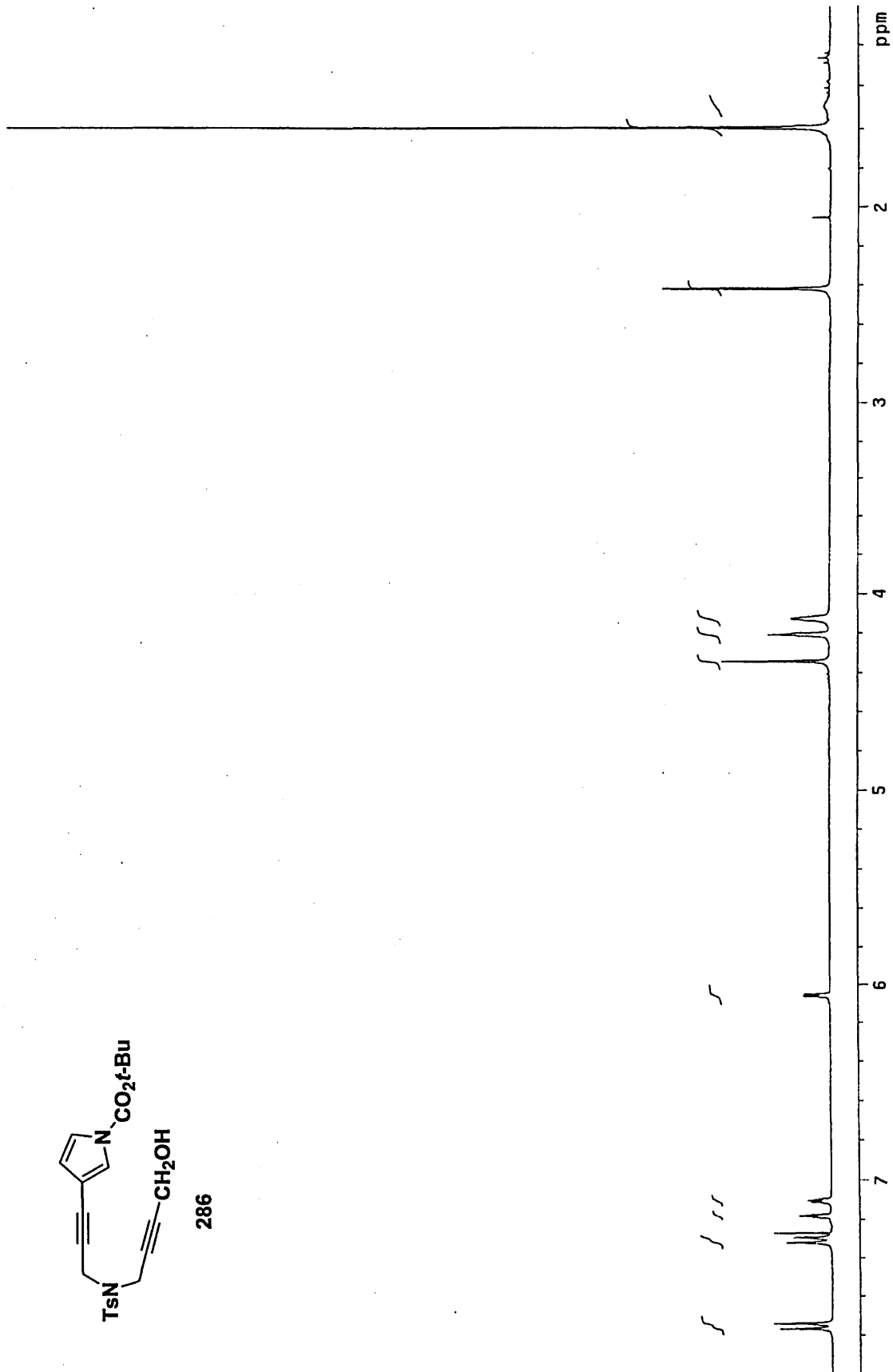


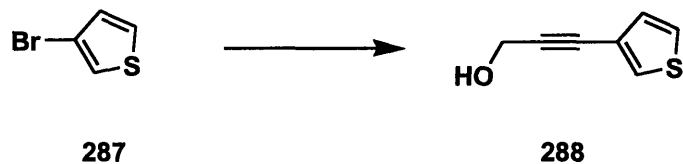


1-(*t*-Butoxycarbonyl)-3-(3-((4-hydroxybut-2-ynyl)[(4-methylphenyl)sulfonyl]amino}prop-1-ynyl)-pyrrole (**286**). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a paraformaldehyde (0.189 g, 6.29 mmol) and 5 mL of THF. A 10-mL, pear-shaped flask fitted with a rubber septum and argon inlet needle was charged with the alkyne **284** (0.504 g, 1.22 mmol) and 5 mL of THF. This solution was cooled to 0 °C and 0.45 mL of EtMgBr solution (3.0 M in diethyl ether, 1.4 mmol) was added dropwise over 1 min. The resulting mixture was stirred at 0 °C for 30 min and then transferred rapidly via cannula into the paraformaldehyde solution (2 mL THF wash). The reaction mixture stirred at rt for 38 h and then diluted with 10 mL of saturated aq NH₄Cl solution and 20 mL of Et₂O. The aqueous phase was separated and extracted with two 10-mL portions of Et₂O, and the combined organic phases were washed with 25 mL of brine, dried over MgSO₄, filtered, and concentrated to furnish 0.700 g of a brown semisolid. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 2 g of silica gel which was added to the top of a column of 60 g of silica gel. Gradient elution with 0-50% EtOAc-hexanes provided 0.276 g (51%) of **286** as an off-white solid: mp 111-112 °C; IR (thin film) 3527, 2235, 1747, and 1597 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.18 (dd, *J* = 2.2, 1.6 Hz, 1 H), 7.11 (dd, *J* = 3.3, 2.2 Hz, 1 H), 6.06 (dd, *J* = 3.3, 1.6 Hz, 1 H), 4.34 (s, 2 H), 4.21 (s, 2 H), 4.13 (s, 2 H), 2.42 (s, 3 H), 1.59 (s, 9 H) and 1.50 (broad s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 148.1, 144.0, 135.3, 129.6, 128.1, 123.9, 120.0, 114.6, 107.1, 84.7, 84.1, 81.4, 80.0, 78.4, 50.9, 37.5, 36.9, 28.0, and 21.6; HRMS (*m/z*): [M+Na⁺] calcd for C₂₃H₂₆N₂O₅S 465.1455; found, 465.1457.



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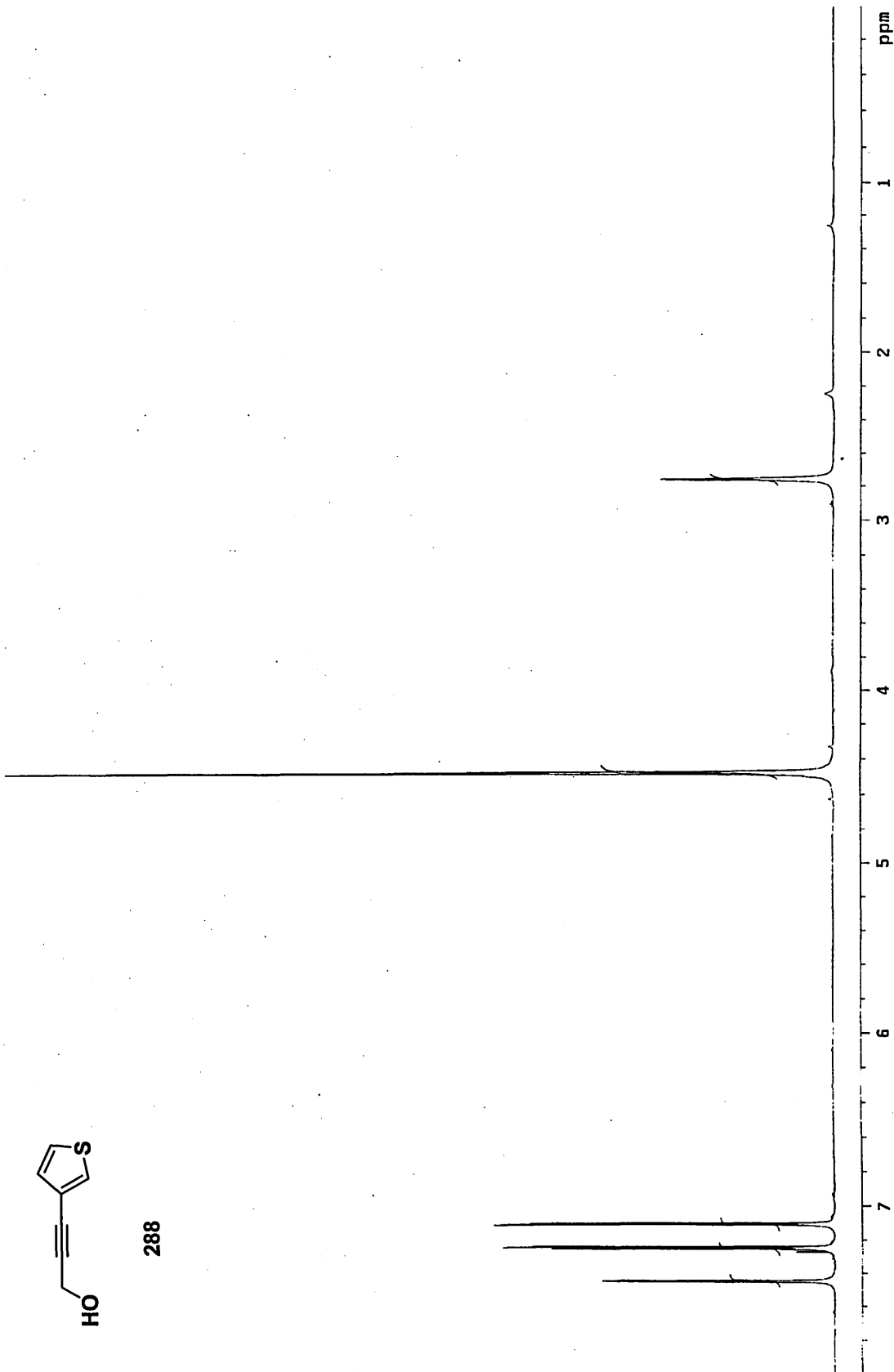


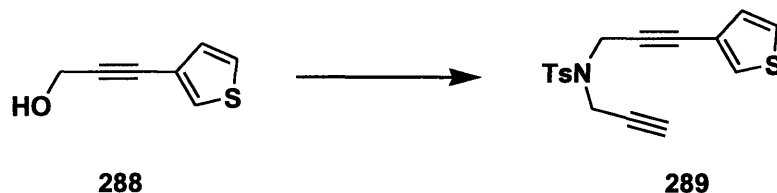


3-(3-Hydroxyprop-1-ynyl)thiophene (288). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with 3-bromothiophene (0.50 mL, 0.87 g, 5.3 mmol), 3 mL of THF, and triethylamine (2.2 mL, 1.6 g, 16 mmol). Pd[(*t*-Bu)₃P]₂ (0.029 g, 0.057 mmol), CuI (0.028 g, 0.15 mmol), and propargyl alcohol (0.40 mL, 0.38 g, 6.8 mmol) were then added, and the resulting mixture was stirred for 72 h at rt and then filtered through 5 g of silica gel in a sintered glass funnel washing with 50 mL of diethyl ether. The filtrate was charged with 1 g of silica gel, concentrated, and the resulting brown powder was added to the top of a column of 10 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes afforded 0.249 g (34%) of **288** as a viscous dark-red oil: IR (thin film) 3335, 2237 and 1519 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.43 (dd, *J* = 3.0, 0.6 Hz, 1 H), 7.23 (dd, *J* = 5.0, 3.0 Hz, 1 H), 7.12 (dd, *J* = 5.0, 0.6 Hz, 1 H), 4.44 (s, 2 H), and 2.59 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 129.9 129.3, 125.5, 121.7, 87.1, 80.9 and 51.6 ; HRMS (*m/z*): [M⁺] calcd for C₇H₆OS 161.0032; found, 161.0031.

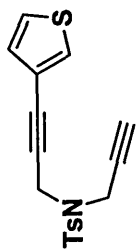


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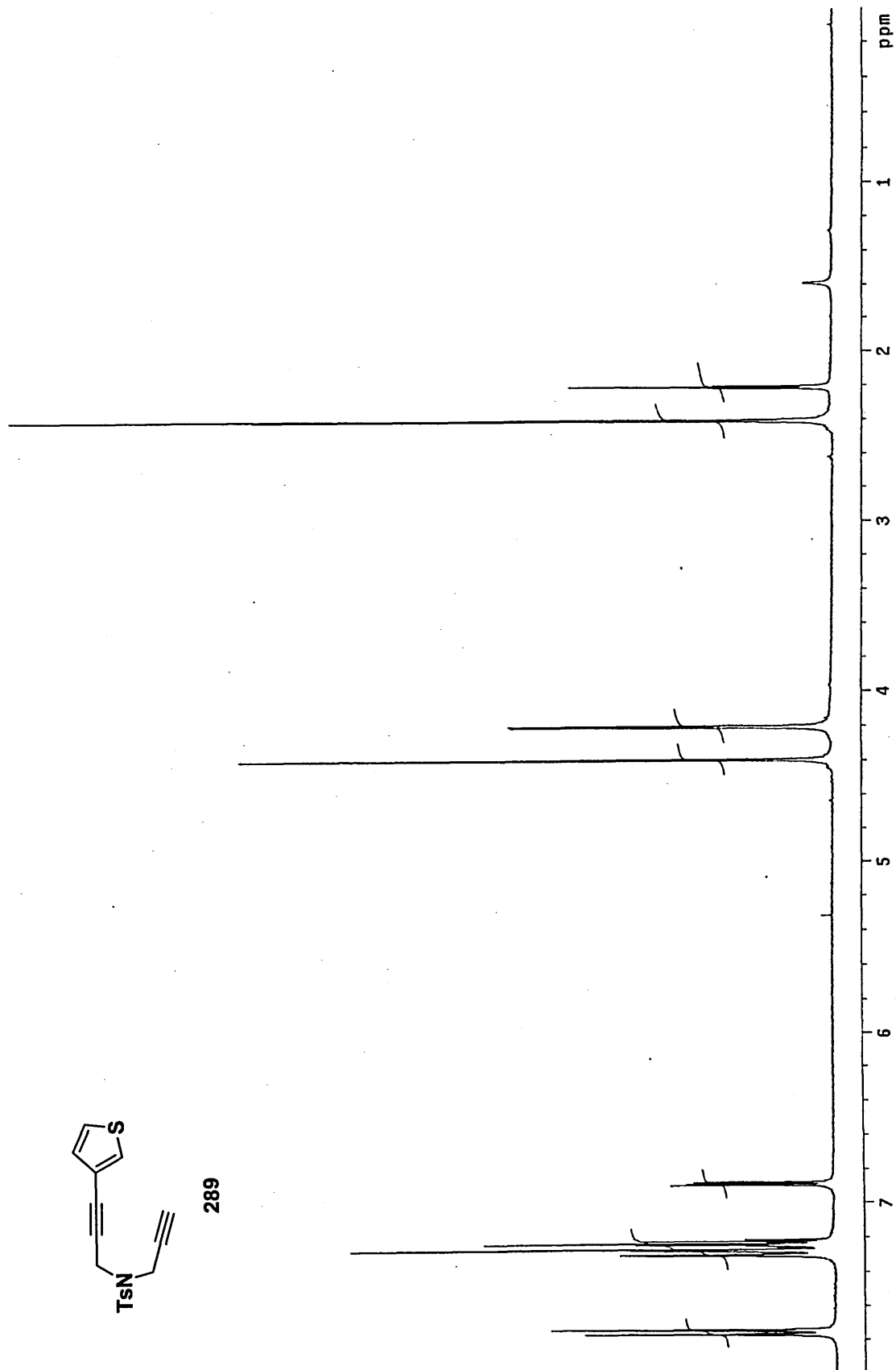


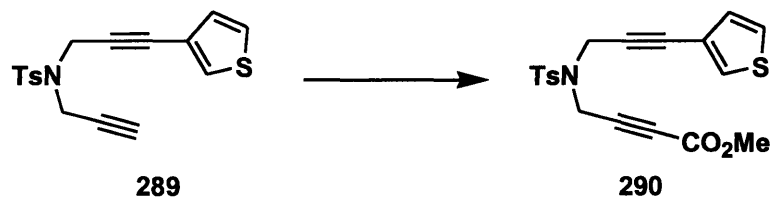


3-(3-[[4-(4-Methylphenyl)sulfonyl]prop-2-ynylamino}prop-1-ynyl)thiophene (289). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of the alcohol **288** (0.354 g, 2.56 mmol) in 12 mL of THF, triphenylphosphine (0.815 g, 3.11 mmol), sulfonamide **229** (0.589 g, 2.82 mmol) and diethyl azodicarboxylate (0.50 mL, 0.56 g, 3.2 mmol). The reaction mixture was stirred at rt for 3 h and then concentrated under reduced pressure to furnish 2.523 g of a brown semisolid. This material was dissolved in 150 mL of CH₂Cl₂ and concentrated onto 5 g of silica gel which was added to the top of a column of 50 g of silica gel. Gradient elution with 0-10% EtOAc-hexanes provided 0.762 g (90%) of **289** an off-white solid: mp 70-72 °C; IR (thin film) 3111, 2224, 1598 and 1350 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 7.24 (dd, *J* = 2.9, 0.6 Hz, 1 H), 7.22 (dd, *J* = 4.9, 2.9 Hz, 1 H), 6.88 (dd, *J* = 4.9, 0.6 Hz, 1 H), 4.39 (s, 2 H), 4.19 (d, *J* = 2.4 Hz, 2 H), 2.39 (s, 3 H), and 2.20 (t, *J* = 2.4 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 144.1, 135.4, 129.8, 129.7, 129.3, 128.1, 125.4, 121.1, 81.2, 81.1, 76.6, 74.2, 37.3, 36.7, and 21.7; HRMS (*m/z*): [M+Na⁺] calcd for C₁₇H₁₅NO₂S 352.0436; found, 352.0440.

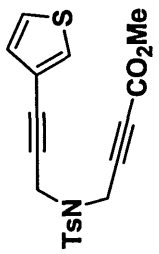


289

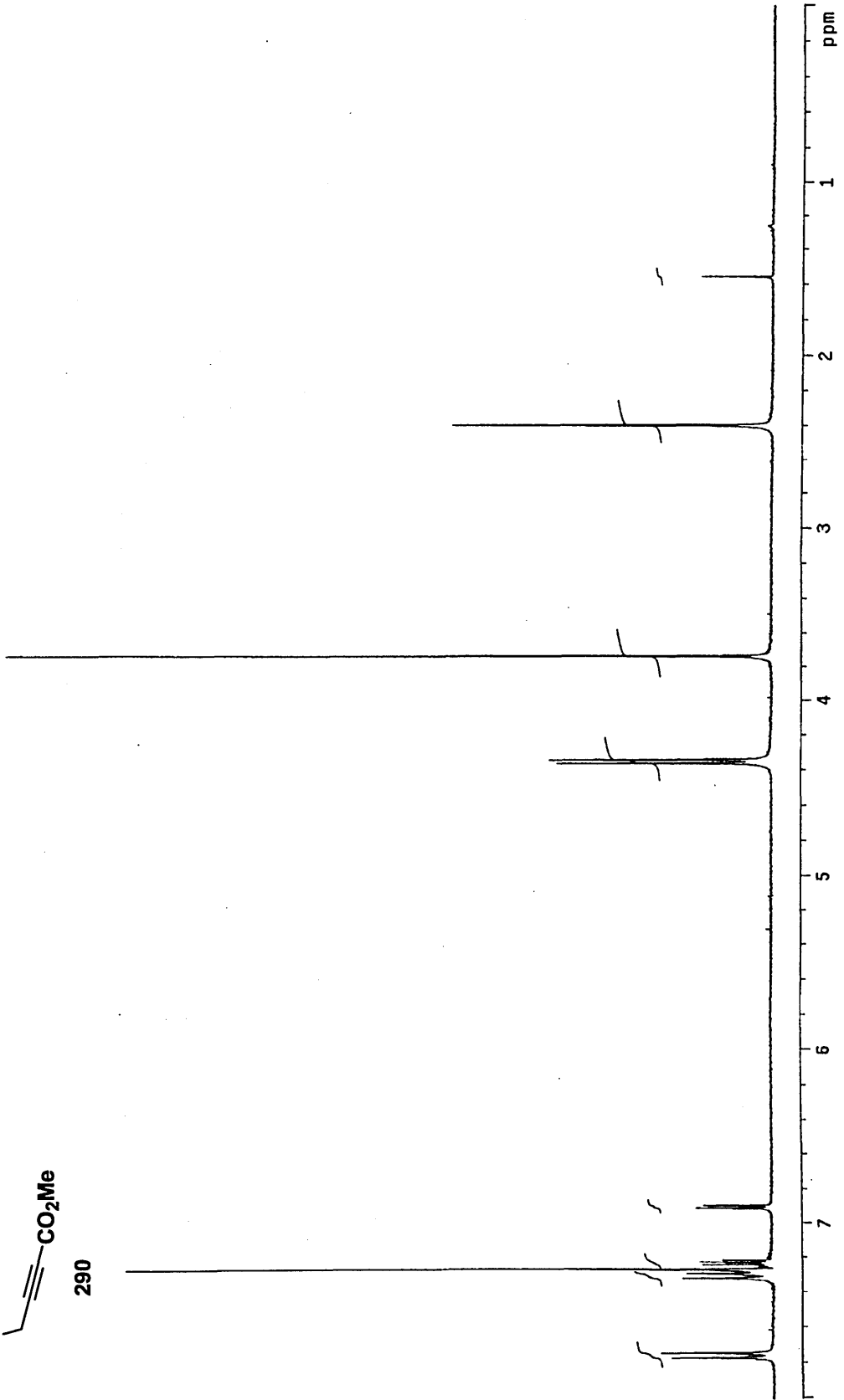


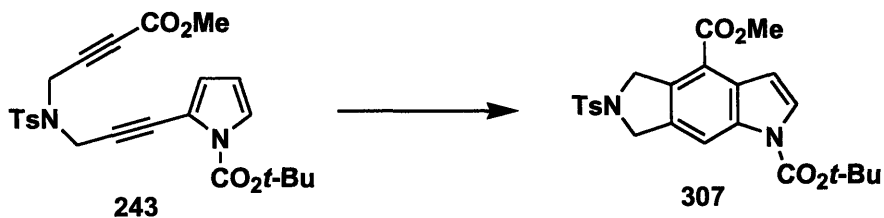


3-(3-((3-Methoxycarbonylbut-2-ynyl))prop-1-ynyl)thiophene (290). A 25-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of the alkyne **289** (0.567 g, 1.72 mmol) in 10 mL of THF. The solution was cooled to 0 °C and 1.0 mL of EtMgCl solution (2.0 M in THF, 2.0 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 0 °C for 30 min, and methyl chloroformate (0.70 mL, 0.86 g, 9.1 mmol) was then added rapidly by syringe. The reaction mixture was allowed to warm to rt, stirred for 17 h, and then diluted with 10 mL of saturated aq NH₄Cl solution and 30 mL of Et₂O. The aqueous phase was separated and extracted with two 20-mL portions of Et₂O, and the combined organic phases were washed 20 mL of brine, dried over MgSO₄, filtered, and concentrated to furnish 0.717 g of a brown semisolid. This material was dissolved in 50 mL of CH₂Cl₂ and concentrated onto 2 g of silica gel which was added to the top of a column of 50 g of silica gel. Gradient elution with 0-10% EtOAc-hexanes provided 0.565 g (85%) of **290** as an off-white solid: mp 83-85 °C; IR (thin film) 2245, 1717, 1598, and 1353 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.26 (dd, *J* = 2.9, 0.6 Hz, 1 H), 7.22 (dd, *J* = 4.9, 2.9 Hz, 1 H), 6.89 (dd, *J* = 4.9, 0.6 Hz, 1 H), 4.36 (s, 2 H), 4.34 (s, 2 H), 3.72 (s, 3 H) and 2.39 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 153.2, 144.4, 134.9, 129.9, 129.8, 129.6, 128.0, 125.5, 121.1, 81.7, 80.64, 80.56, 77.2, 53.0, 37.9, 36.7, and 21.7; HRMS (*m/z*): [M+Na⁺] calcd for C₁₉H₁₇NO₄S₂ 410.0491; found, 410.0488.

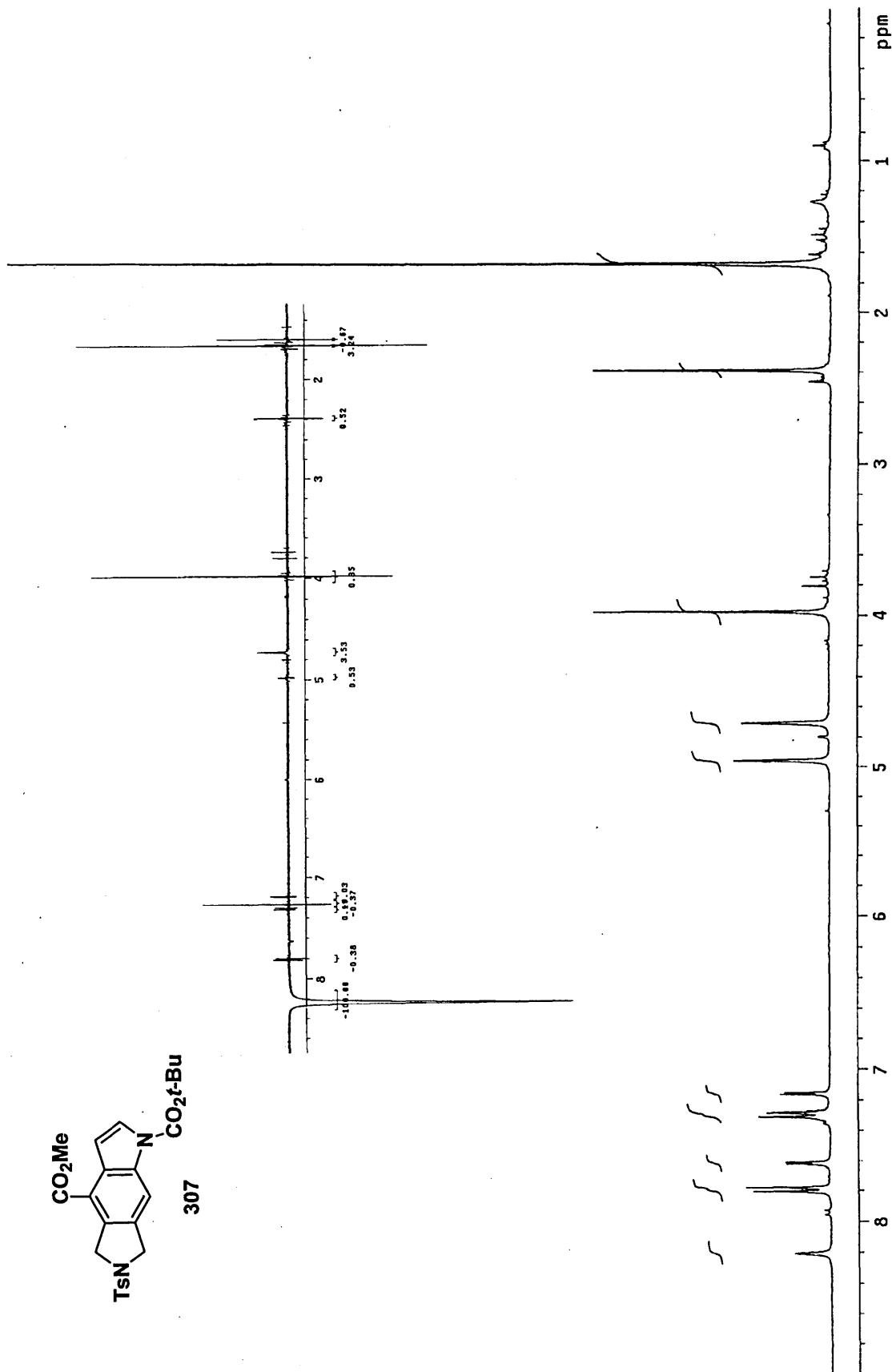
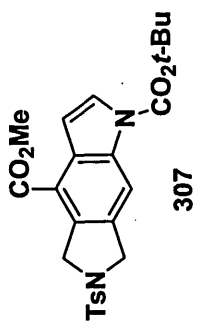


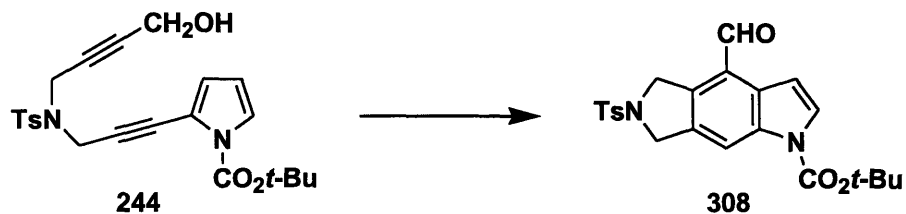
290



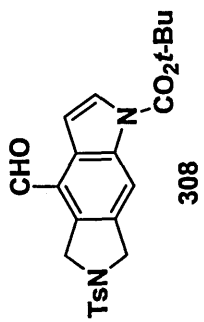


1-(*t*-Butoxycarbonyl)-4-carbomethoxy-6-[(4-methylphenyl)sulfonyl]-3-pyrrolino[3,4-*f*]indole (**307**). A 50-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with the ester **243** (0.293 g, 0.623 mmol), 2,6-di-*t*-butyl-4-methylphenol (0.256 g, 1.16 mmol) and 12.5 mL of benzene. The reaction mixture was heated at reflux for 15 h, allowed to cool to room temperature, and then concentrated under reduced pressure to furnish 0.5 g of a dark-brown oil that was dissolved in 50 mL of CH₂Cl₂ and concentrated onto 5 g of silica gel which was added to the top of a column of 45 g of silica gel. Gradient elution with 0-20% EtOAc-hexanes provided 0.166 g (57%) of **307** as a light-brown viscous oil: IR (thin film) 1736, 1598, and 1581 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.21 (s, 1 H), 7.80 (d, *J* = 8.2 Hz, 2 H), 7.62 (d, *J* = 3.8 Hz, 1 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.16 (d, *J* = 3.8 Hz, 1 H), 4.96 (s, 2 H), 4.71 (s, 2 H), 3.98 (s, 3 H), 2.39 (s, 3 H), and 1.67 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 166.5, 149.2, 143.6, 136.0, 134.3, 133.7, 133.4, 130.6, 129.9, 128.0, 127.6, 116.7, 113.7, 108.1, 84.6, 55.2, 53.4, 52.2, 28.4, and 21.8; HRMS (*m/z*): [M+Na⁺] calcd for C₂₄H₂₆N₂O₆S 493.1404; found, 493.1417.

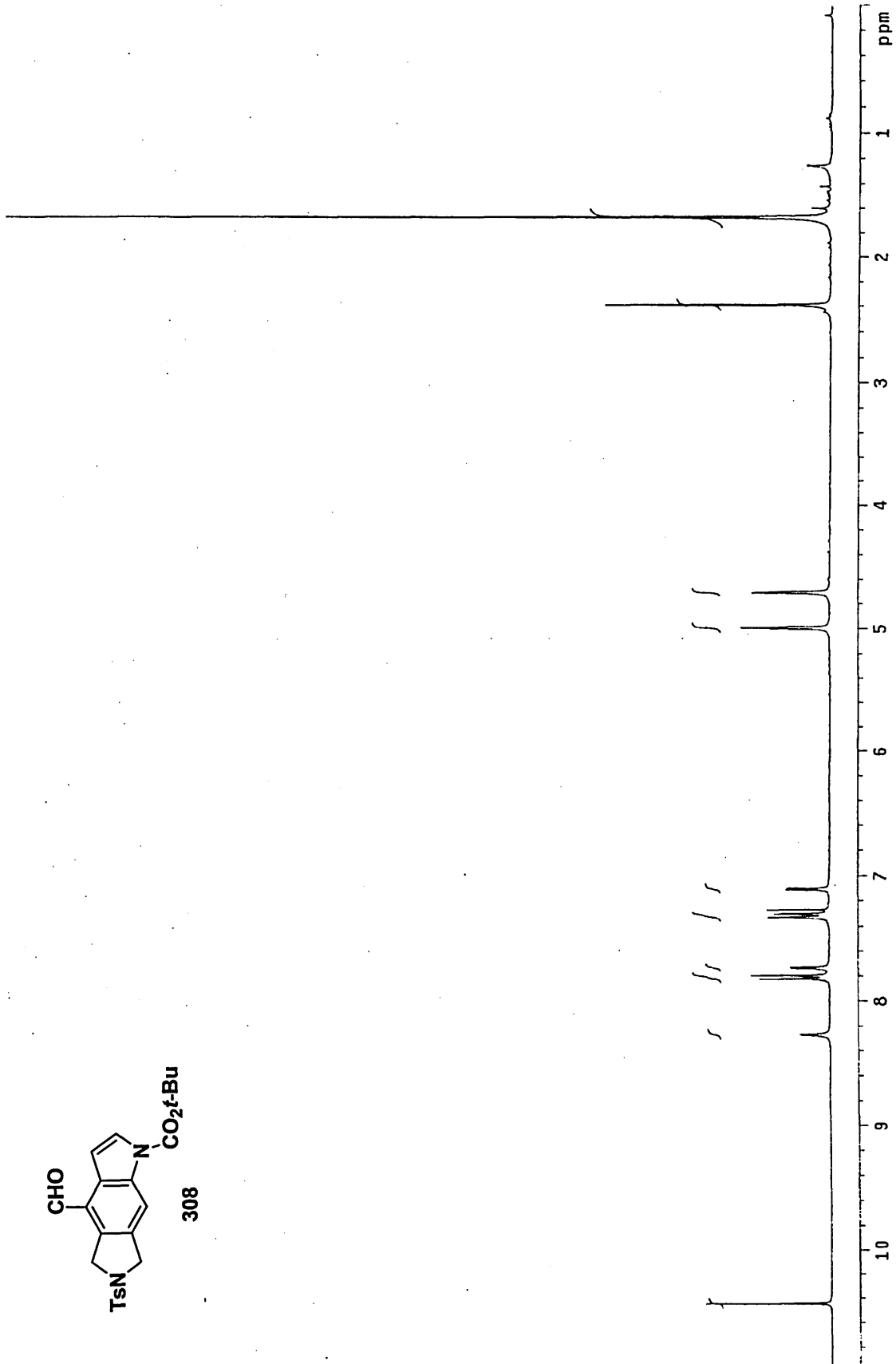


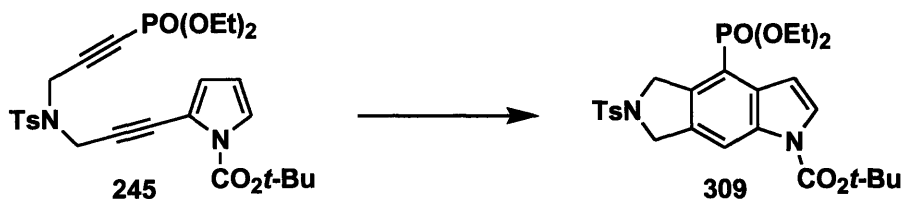


1-(*t*-Butoxycarbonyl)-4-formyl-6-[(4-methylphenyl)sulfonyl]-3-pyrrolo[3,4-*f*]indole (308). A 25-mL, round-bottomed flask fitted with an argon inlet adapter was charged with the alcohol **244** (0.132 g, 0.298 mmol), 6 mL of CH₂Cl₂, and Dess-Martin periodinane (0.190 g, 0.447 mmol). After stirring at rt for 29 h, the reaction mixture was diluted with 10 mL of half-saturated NaHCO₃ solution and 10 mL of CH₂Cl₂. The aqueous phase was separated and extracted with 10 mL of CH₂Cl₂, and the combined organic phases were then washed with two 20-mL portions of half-saturated NaHCO₃ solution (each of the separated aqueous phases was individually extracted with 10 mL of CH₂Cl₂). The combined organic phases were dried over MgSO₄, filtered, and concentrated to furnish 0.176 g of dark-yellow oil. This material was dissolved in CH₂Cl₂ and concentrated onto 0.5 g of silica gel which was added to the top of a 15-g column of silica gel. Gradient elution with 0-10% EtOAc-hexanes provided 0.071 g (54%) of **308** as a yellow solid: mp 154-156 °C; IR (film) 1736, 1687, 1598, 1582, and 1138 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.44 (s, 1 H), 8.27 (s, 1 H), 7.81 (d, *J* = 8.2 Hz, 2 H), 7.73 (d, *J* = 3.8 Hz, 1 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 7.11 (d, *J* = 3.8 Hz, 1 H), 4.99 (s, 2 H), 4.71 (s, 2 H), 2.39 (s, 3 H), and 1.67 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 149.3, 143.9, 136.3, 133.9, 133.8, 133.6, 131.5, 130.1, 129.5, 127.8, 121.8, 115.2, 105.7, 104.5, 85.1, 53.7, 52.9, 38.3, 32.9, 28.3, and 21.7; HRMS (*m/z*): [M+Na⁺] calcd for C₂₃H₂₄N₂O₅S 463.1298; found, 463.1304.

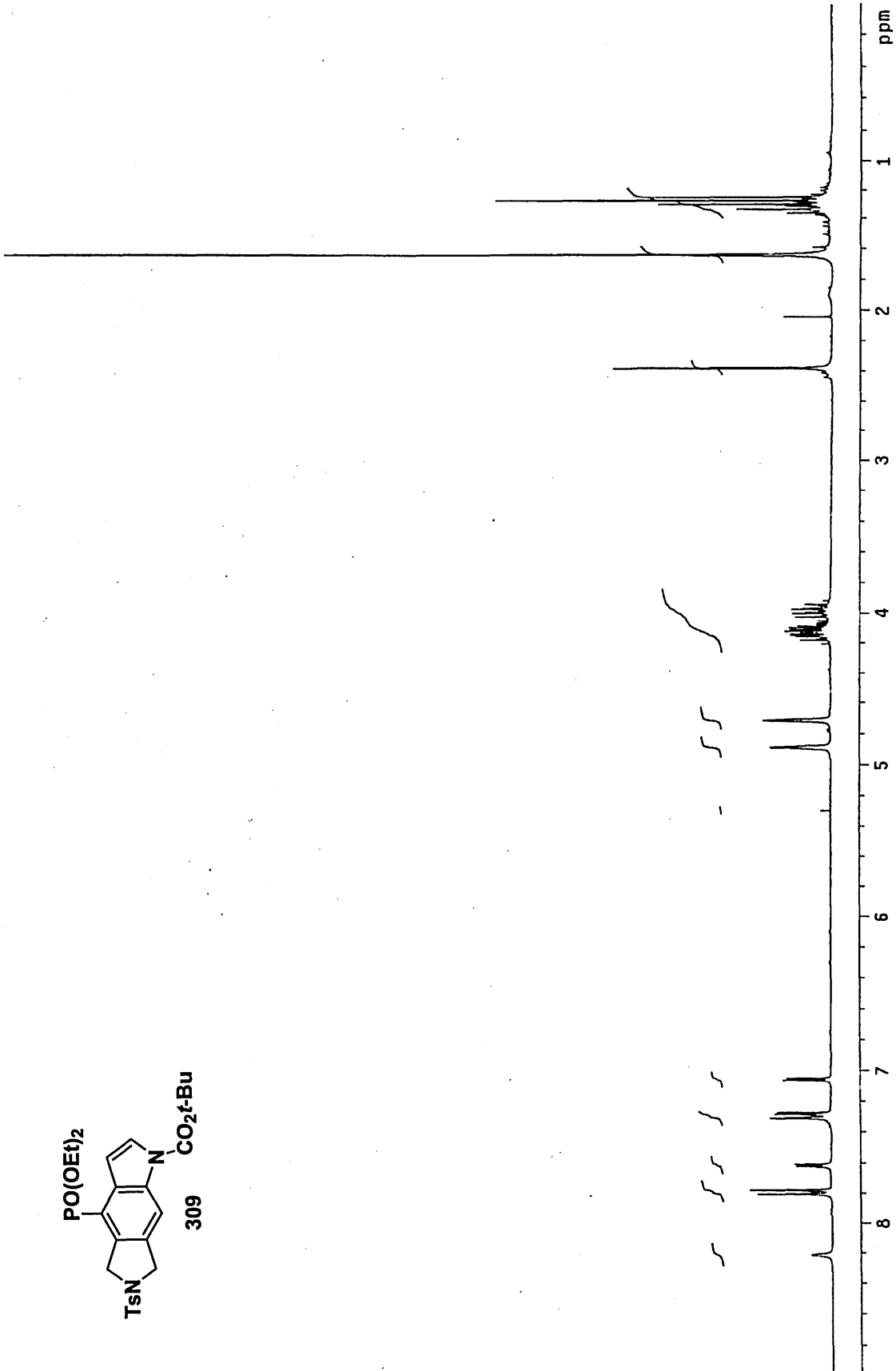
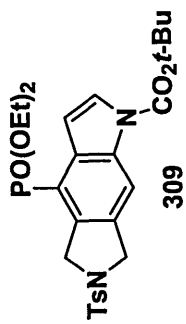


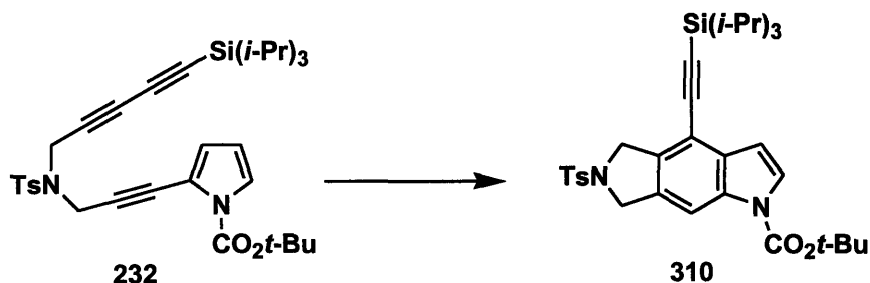
308



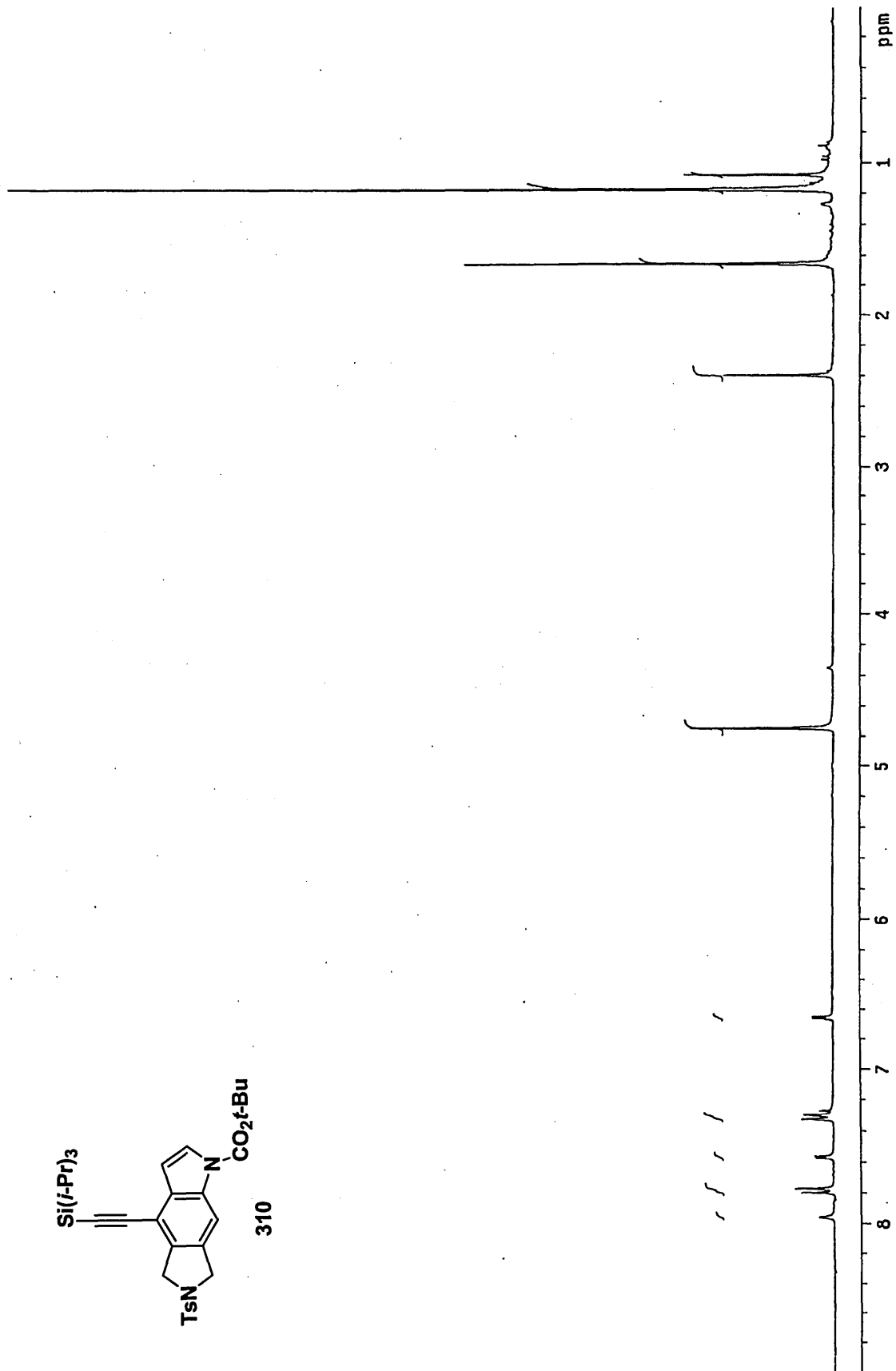
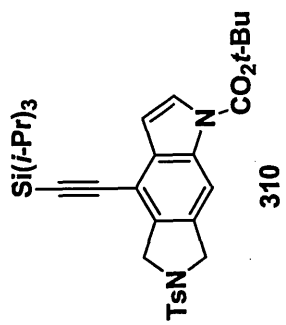


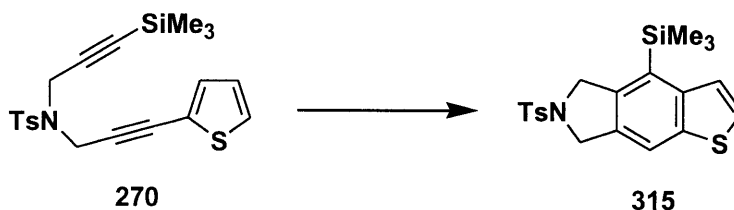
1-(*t*-Butoxycarbonyl)-4-(bisethoxyphosphoryl)-6-[(4-methylphenyl)sulfonyl]-3-pyrrolino[3,4-*f*]indole (309). A threaded Pyrex tube (ca. 25 mL capacity) was charged with the phosphonate **245** (0.281 g, 0.512 mmol), BHT (0.338 g, 1.53 mmol), and 10 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed under argon with a threaded Teflon cap. The reaction mixture was heated in an oil bath at 130 °C for 6 h, allowed to cool to rt, transferred to a 25-mL round-bottomed flask with the aid of 10 mL of CH₂Cl₂, and concentrated under reduced pressure to furnish 0.653 g of a black oil. This material was immediately redissolved in CH₂Cl₂ and concentrated onto 3 g of silica gel which was added to the top of a 27-g column of silica gel. Gradient elution with 50-100% EtOAc-hexanes yielded 0.171 g (61%) of **309** as a dark-brown viscous oil: IR (thin film) 1738, 1598, 1576, and 1257 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.21 (s, 1 H), 7.79 (d, *J* = 8.2 Hz, 2 H), 7.62 (d, *J* = 3.8 Hz, 1 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.06 (d, *J* = 3.8 Hz, 1 H), 4.89 (s, 2H), 4.71 (s, 2 H), 4.21-4.02 (m, 2 H), 4.02-.3.91 (m, 2 H), 2.38 (s, 3 H), 1.64 (s, 9 H), and 1.40-1.08 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 149.4, 143.8, 136.0, 135.9, 133.7, 133.4, 133.3, 130.0, 127.9, 113.6, 112.9, 107.8, 84.6, 62.2, 54.3, 53.5, 28.3, 21.7, and 16.5; HRMS (*m/z*): [M+Na⁺] calcd for C₂₆H₃₃N₂O₇PS 571.1638; found, 571.1632.



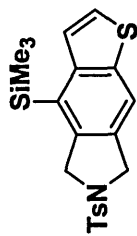


1-(*t*-Butoxycarbonyl)-4-(triisopropylsilyl)ethynyl-6-[(4-methylphenyl)sulfonyl]-3-pyrrolino[3,4-*f*]indole (**310**). A 50-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with the diyne **232** (0.316 g, 0.532 mmol), BHT (0.352 g, 1.60 mmol) and 11 mL of benzene. The reaction mixture was heated at reflux for 2 h, allowed to cool to room temperature, and then concentrated under reduced pressure to furnish 0.7 g of a dark-brown oil that was dissolved in CH₂Cl₂ and concentrated onto 5 g of silica gel which was added to the top of a column of 45 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes provided 0.152 g (48%) of **310** as a brown viscous oil: IR (thin film) 2149, 1737, 1598 and 1139 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.96 (s, 1 H), 7.78 (d, *J* = 8.2 Hz, 2 H), 7.57 (d, *J* = 3.8 Hz, 1 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 6.66 (d, *J* = 3.8 Hz, 1 H), 4.75 (s, 4 H), 2.39 (s, 3 H), 1.67 (s, 9 H), 1.18 (s, 21 H); ¹³C NMR (75 MHz, CDCl₃) δ 149.5, 143.8, 134.0, 133.8, 132.6, 132.3, 130.0, 127.8, 127.1, 110.2, 109.8, 106.5, 101.7, 98.9, 84.5, 54.5, 53.7, 28.3, 21.6, 18.9, 18.7, 11.4; HRMS (*m/z*): [M+Na⁺] calcd for C₃₃H₄₄N₂O₄SSi 615.2683; found, 615.2692.

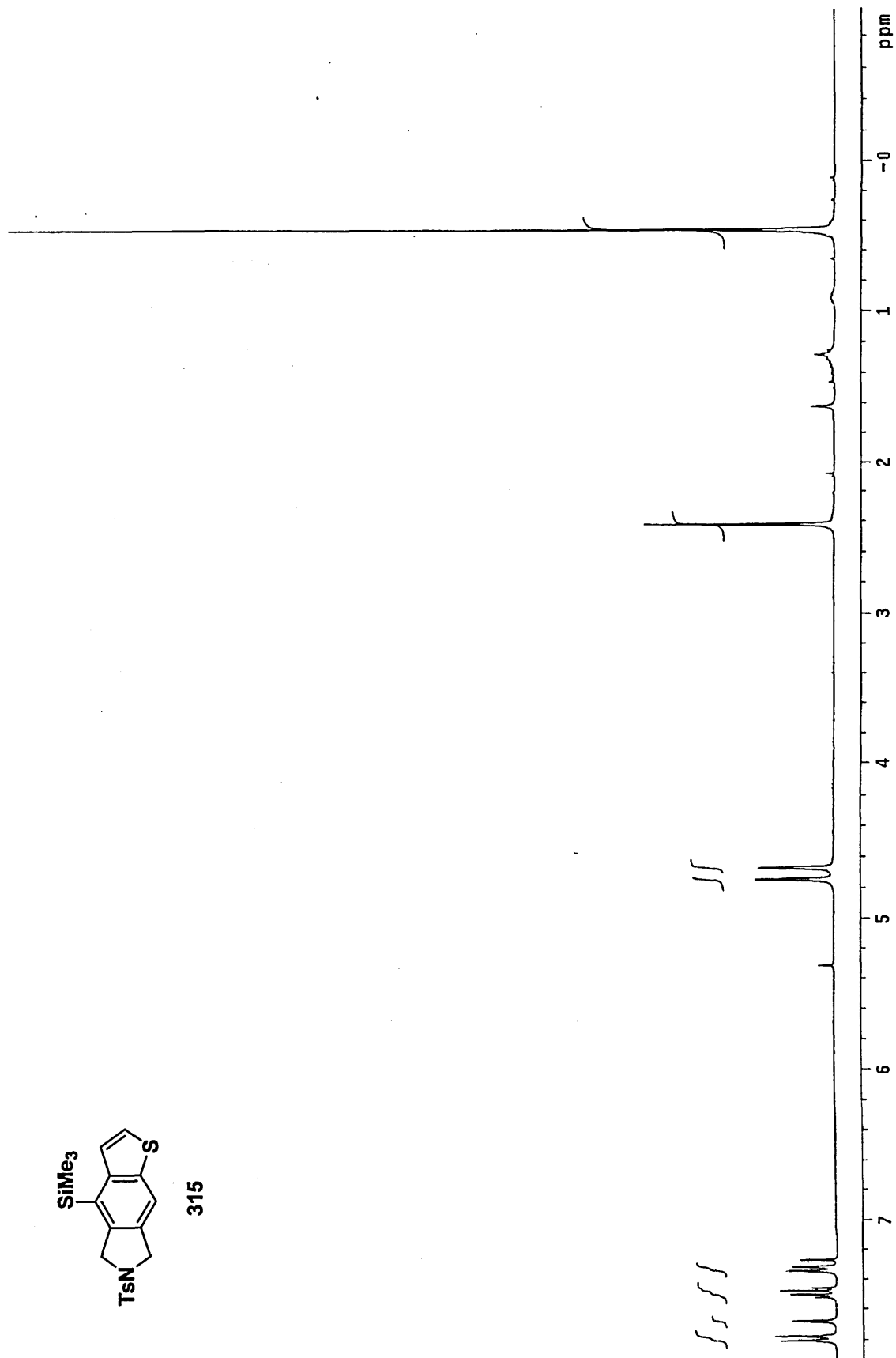


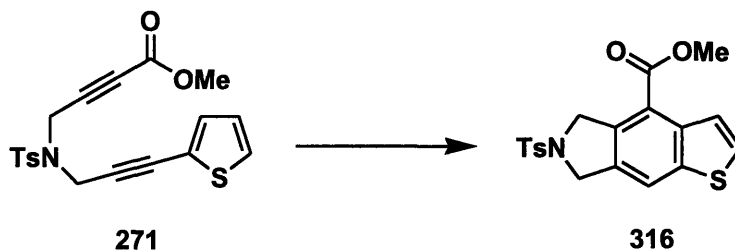


6-[(4-Methylphenyl)sulfonyl]-4-trimethylsilylthiopheno[3,2-f]isoindoline (315). A threaded Pyrex tube (ca. 25 mL capacity) was charged with alkynyl silane **270** (0.129 g, 0.321 mmol), BHT (0.210 g, 0.953 mmol), and 6.5 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed under argon with a threaded teflon cap. The reaction mixture was heated in an oil bath at 150 °C for 44 h, allowed to cool to rt, transferred to a 50-mL round-bottomed flask with the aid of 30 mL of CH₂Cl₂, and concentrated under reduced pressure to furnish 0.354 g of a black oil. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 1 g of silica gel which was added to the top of a column of 10 g of silica gel. Gradient elution with 0-1% EtOAc-hexanes yielded 0.103 g (80%) of **315** as a light-brown oil: IR (thin film) 1598 and 1347 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.79 (d, *J* = 8.2 Hz, 2 H), 7.78 (s, 1 H), 7.51 (d, *J* = 5.5 Hz, 1 H), 7.48 (d, *J* = 5.5 Hz, 1 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 4.74 (s, 2 H), 4.66 (s, 2 H), 2.41 (s, 3 H) and 0.44 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 144.0, 143.6, 139.6, 133.6, 132.5, 130.0, 129.3, 127.9, 126.7, 124.7, 117.6, 54.9, 52.8, 21.7, and 1.6; HRMS (*m/z*): [M+Na⁺] calcd for C₂₀H₂₃NO₂SSi 424.0832; found, 424.0848.



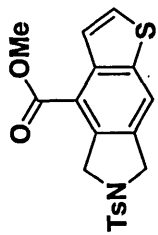
315



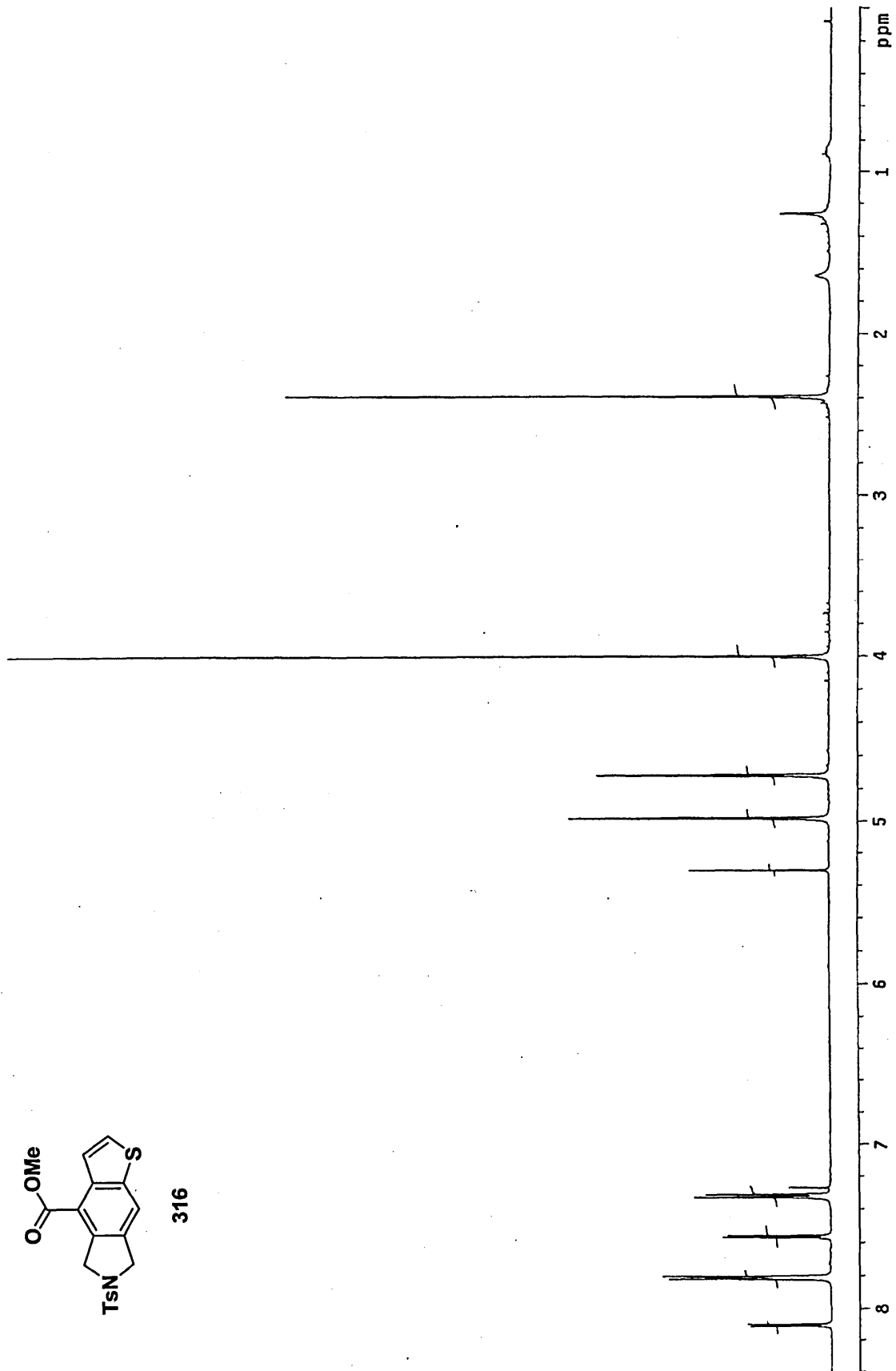


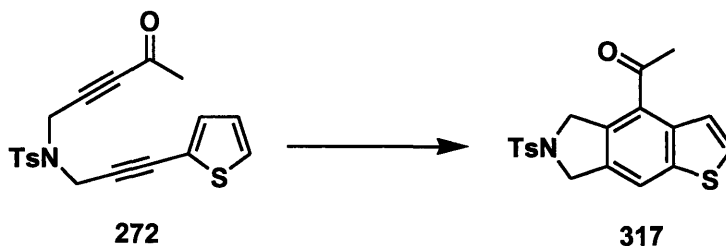
4-Carbomethoxy-6-[(4-methylphenyl)sulfonyl]thiopheno[3,2-f]isoindoline (316). A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ester **271** (0.118 g, 0.304 mmol), BHT (0.134 g, 0.601 mmol) and 6 mL of toluene. The reaction mixture was heated at reflux for 6 h, allowed to cool to room temperature, and then concentrated under reduced pressure to furnish 0.123 g of a dark-brown oil that was dissolved in 10 mL of CH₂Cl₂ and concentrated onto 1 g of silica gel which was added to the top of a column of 20 g of silica gel. Gradient elution with 0-20% EtOAc-hexanes provided 0.083 g (70%) of **316** as a light-brown viscous oil: IR (thin film) 1710, 1597, 1347 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.10 (d, *J* = 5.6 Hz, 2 H), 7.86-7.77 (m, 3 H), 7.56 (d, *J* = 5.6 Hz, 1 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 7.16 (d, *J* = 3.8 Hz, 1 H), 4.98 (s, 2 H), 4.72 (s, 2 H), 4.00 (s, 3 H), and 2.39 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 166.6, 144.0, 141.4, 138.8, 137.3, 133.8, 133.2, 130.1, 129.1, 127.8, 124.8, 120.9, 120.0, 55.2, 52.9, 52.4, and 21.7; HRMS (*m/z*): [M+Na⁺] calcd for C₁₉H₁₇NO₄S₂ 410.0491; found, 410.0503.

Lewis acid-catalyzed procedure: A 25-mL, round-bottomed fitted with a rubber septum and argon inlet needle was charged with ester **271** (0.266 g, 0.583 mmol) and 12 mL of dichloromethane. The reaction mixture was cooled to 0 °C and 0.30 mL of dimethylaluminum chloride solution (1.0 M in hexanes, 0.30 mmol) was added dropwise over 1 min. The reaction mixture was stirred at rt for 9 h, and then diluted with 20 mL of saturated aq NaHCO₃ solution and 50 mL of ether. The aqueous phase was separated and extracted with three 20-mL portions of ether, and the combined organic phases were dried over MgSO₄, filtered, and concentrated to provide 0.200 g (88%) of pure **316**.

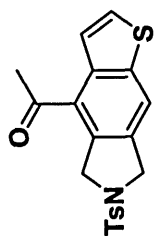


316

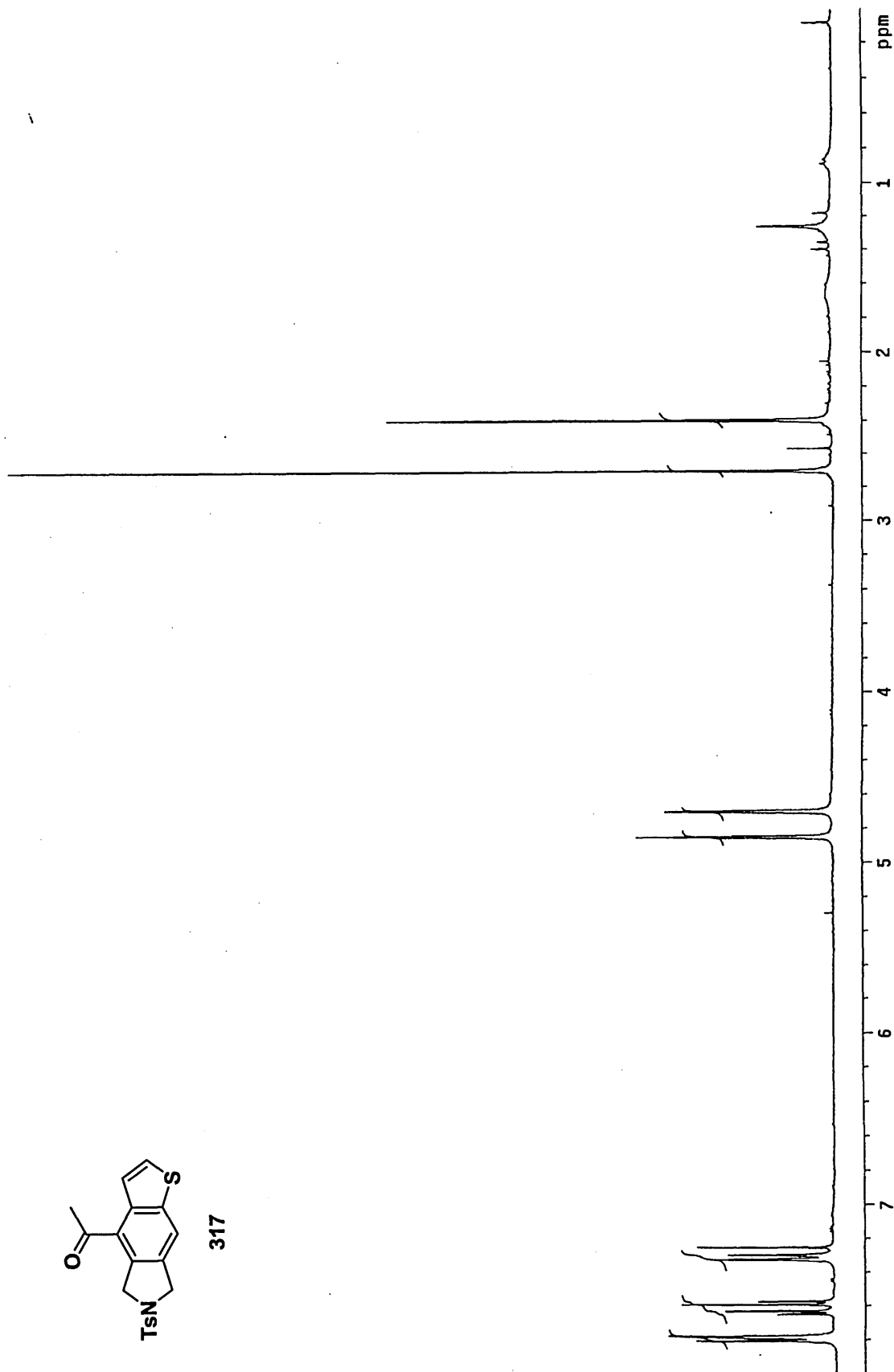


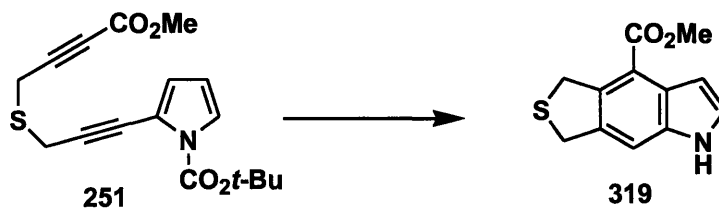


6-[(4-Methylphenyl)sulfonyl]-4-(1-oxoethyl)thiopheno[3,2-f]isoindoline (317). A threaded Pyrex tube (ca. 25 mL capacity) was charged with alkyne ketone **272** (0.271 g, 0.731 mmol) and 15 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed under argon with a threaded teflon cap. The reaction mixture was heated in an oil bath at 150 °C for 17 h, allowed to cool to rt, transferred to a 50-mL round-bottomed flask with the aid of 20 mL of CH₂Cl₂, and concentrated under reduced pressure to furnish 0.293 g of a black oil. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 1 g of silica gel which was added to the top of a column of 20 g of silica gel. Gradient elution with 0-10% EtOAc-hexanes yielded 0.110 g (41%) of **317** as a light-yellow solid: mp 160-162 °C; IR (thin film) 1675, 1597 and 1349 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.82 (d, *J* = 8.1 Hz, 2 H), 7.81 (s, 1 H), 7.66 (d, *J* = 5.6 Hz, 1 H), 7.60 (d, *J* = 5.6 Hz, 1 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 4.96 (s, 2 H), 4.71 (s, 2 H), 2.71 (s, 3 H), and 2.40 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 188.2, 144.1, 141.5, 136.9, 134.4, 134.0, 133.5, 130.1, 129.6, 127.9, 123.1, 120.1, 54.5, 52.8, 31.8, and 21.7; HRMS (*m/z*) [M+Na⁺] calcd for C₁₉H₁₇NO₃S₂ 394.0542; found, 394.0556.

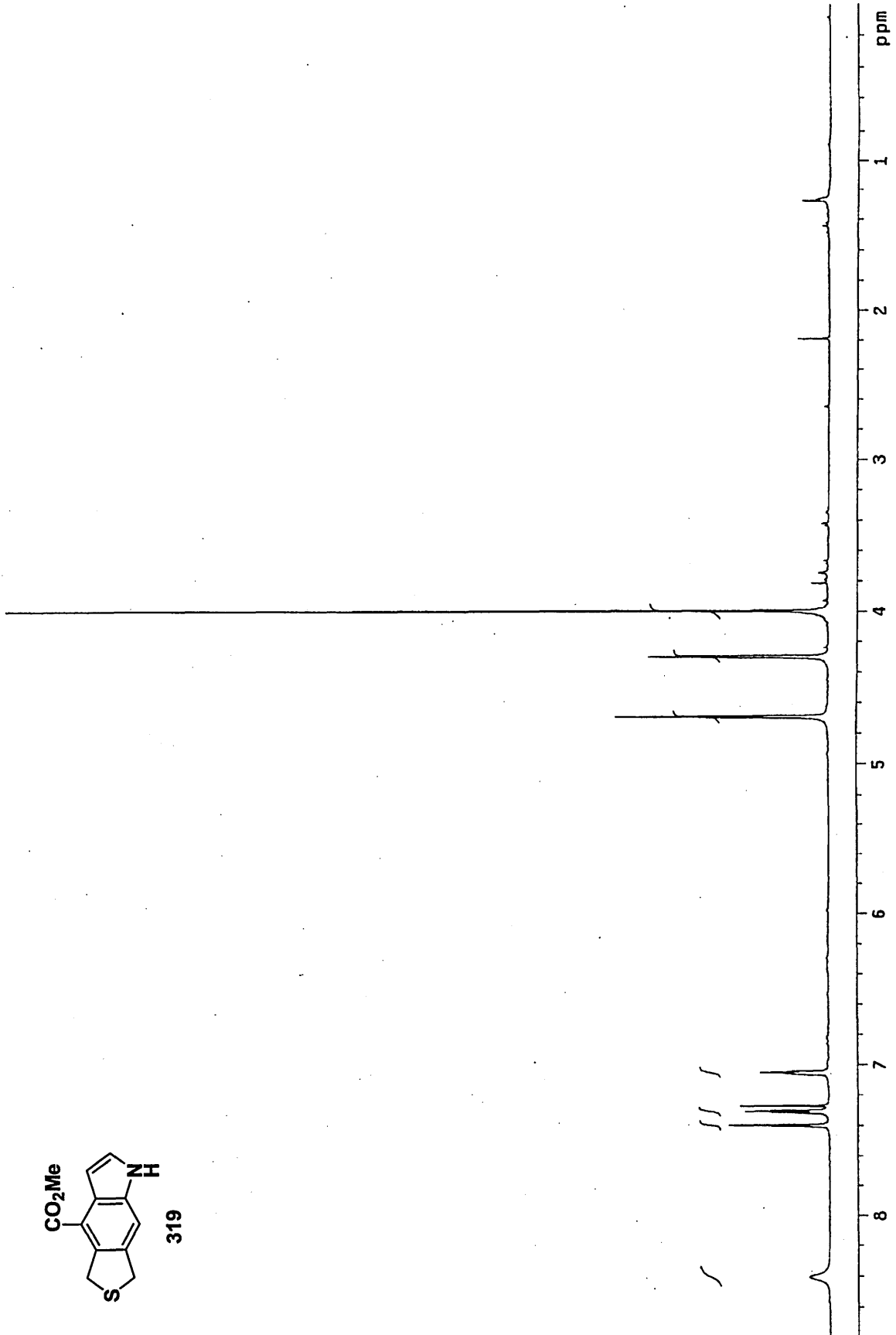
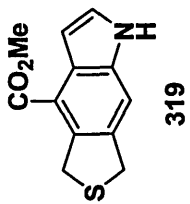


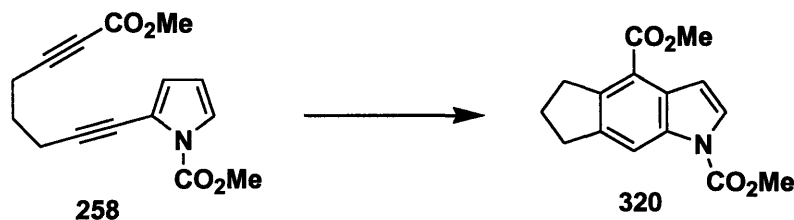
317





4-Carbomethoxy-5,7-dihydrothiopheno[3,4-f]indole (319). A threaded Pyrex tube (ca. 25 mL capacity) was charged with ester **251** (0.148 g, 0.443 mmol), BHT (0.293 g, 1.33 mmol), and 10 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed under argon with a threaded teflon cap. The reaction mixture was heated in an oil bath at 180 °C for 5 h, allowed to cool to rt, transferred to a 25-mL round-bottomed flask with the aid of 10 mL of CH₂Cl₂, and concentrated under reduced pressure to furnish 0.498 g of a black oil. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 5 g of silica gel which was added to the top of a column of 45 g of silica gel. Gradient elution with 0-20% EtOAc-hexanes yielded 0.048 g (46%) of **319** as a brown solid: mp 144-146 °C; IR (thin film) 3348, 1681, 1620, and 1564 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.40 (s, 1 H), 7.40 (s, 1 H), 7.34-7.28 (m, 1 H), 7.09-7.03 (m, 1 H), 4.69 (s, 2 H), 4.30 (s, 2 H), and 4.00 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 168.3, 136.9, 136.5, 136.4, 127.4, 126.8, 117.7, 111.4, 104.4, 51.9, 38.5, and 36.8; HRMS (*m/z*): [M+Na⁺] calcd for C₁₂H₁₁NO₂S 256.0403; found, 256.0411.

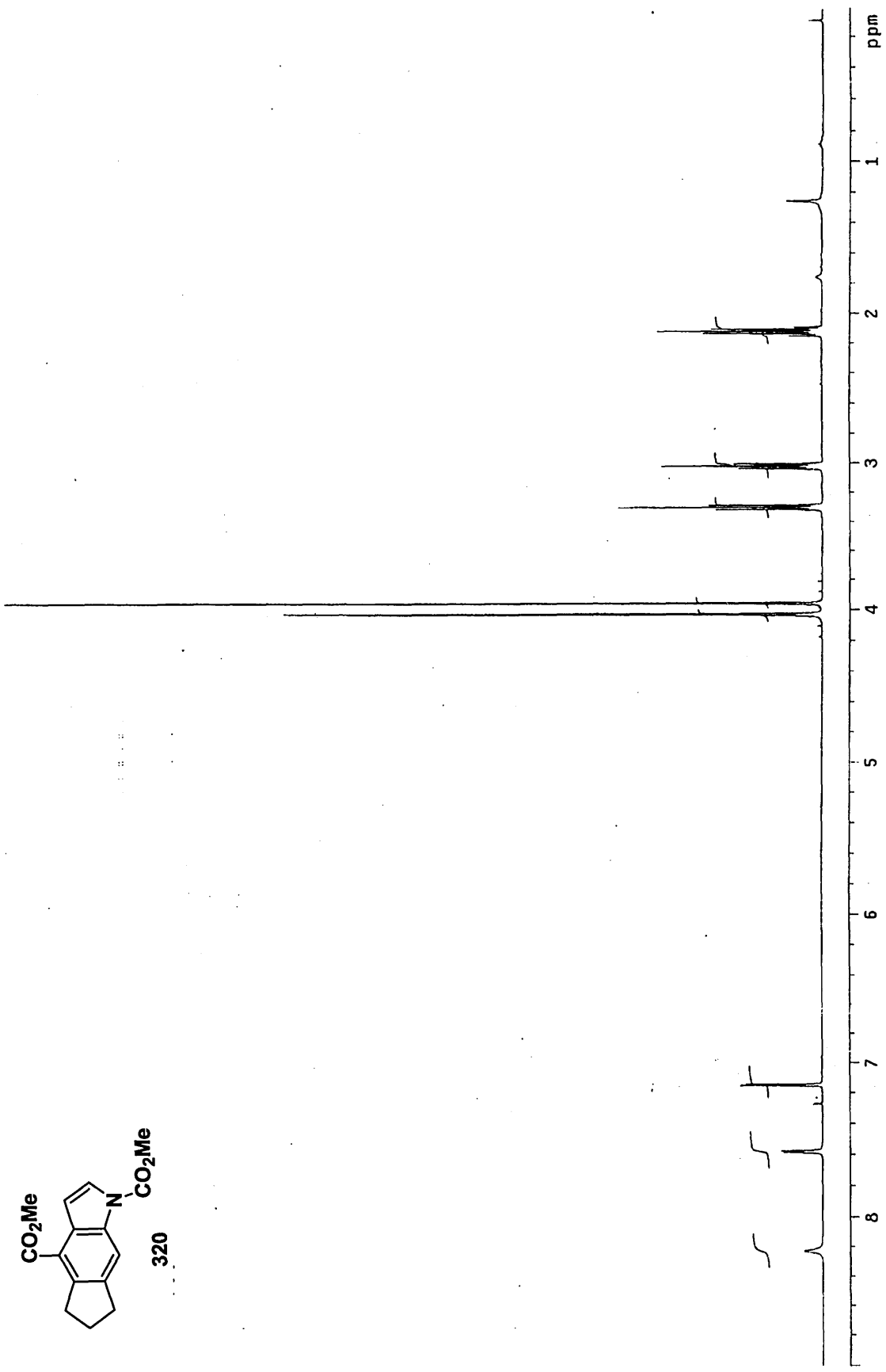
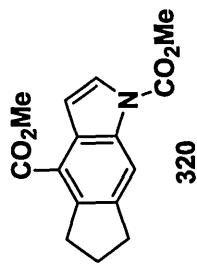


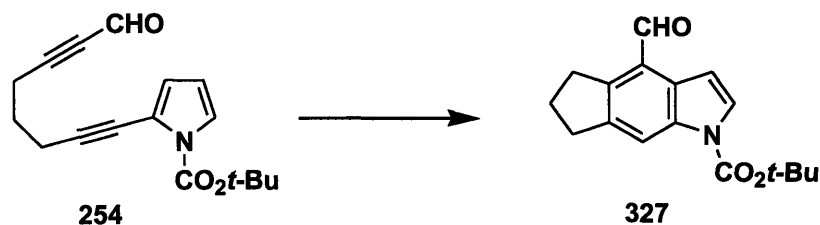


1,4-(Biscarbomethoxy)-5,6,7-trihydrocyclo-penta[1,2-f]indole (320).

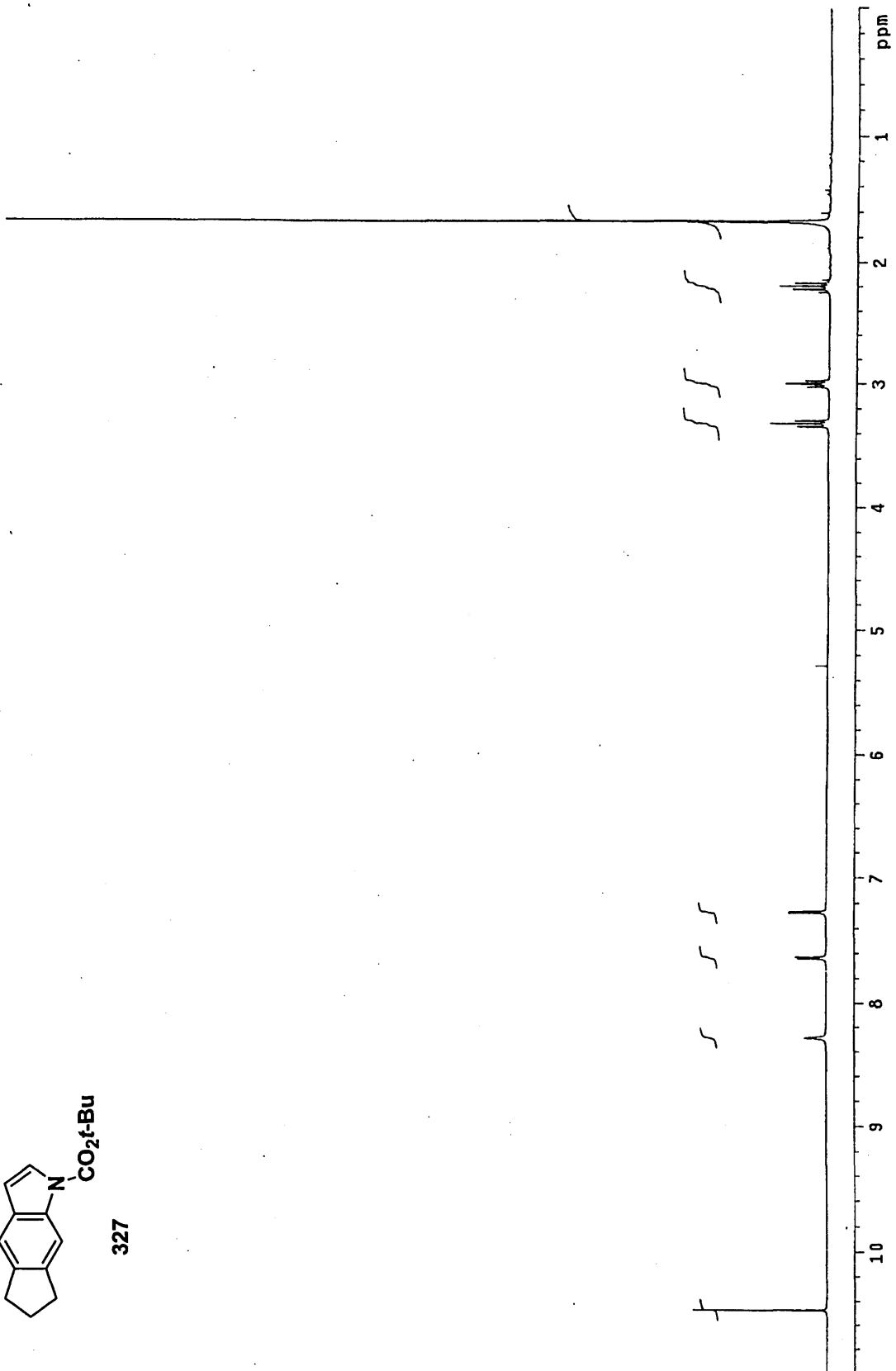
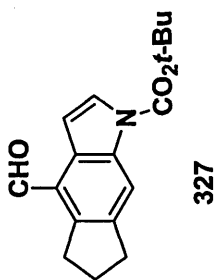
A threaded Pyrex tube (ca. 10 mL capacity) was charged with ester **258** (0.068 g, 0.25 mmol), BHT (0.163 g, 0.741 mmol), and 5 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed under argon with a threaded teflon cap. The reaction mixture was heated in an oil bath at 180 °C for 27 h, allowed to cool to rt, transferred to a 25-mL round-bottomed flask with the aid of 10 mL of CH₂Cl₂, and concentrated under reduced pressure to furnish 0.229 g of a black oil. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 0.5 g of silica gel which was added to the top of a column of 15 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes yielded 0.045 g (67%) of **320** as a light-yellow solid: mp 87-90 °C; IR (thin film) 1741, 1713 1607 and 1574 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.25 (s, 1 H), 7.60 (d, *J* = 3.9 Hz, 1 H), 7.16 (d, *J* = 3.9 Hz, 1 H), 4.04 (s, 3 H), 3.97 (s, 3 H), 3.32 (t, *J* = 7.4 Hz, 2 H), 3.04 (t, *J* = 7.4 Hz, 2 H), and 2.13 (quint, *J* = 7.4 Hz, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 168.1, 151.6, 143.3, 142.8, 135.4, 129.6, 126.2, 118.3, 115.3, 109.3, 54.1, 51.8, 34.1, 33.1, and 25.9; HRMS (*m/z*): [M+Na⁺] calcd for C₁₅H₁₅NO₄ 296.0899; found, 296.0893.

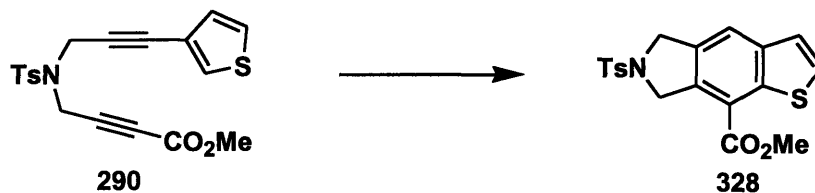
Lewis acid-catalyzed procedure: A 50-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with alkynyl ester **258** (0.254 g, 0.931 mmol) and 20 mL of dichloromethane, and to the resulting solution was added 2.3 mL of MeAlCl₂ solution (1.0 M in hexanes, 2.3 mmol) dropwise over 1 min. The reaction mixture was stirred at rt for 48 h, and then diluted with 50 mL of saturated aq NaHCO₃ solution and 100 mL of ether. The aqueous phase was separated and extracted with three 50-mL portions of ether, and the combined organic phases were dried over MgSO₄, filtered, and concentrated to give 0.276 g of a dark-brown semisolid that was dissolved in 20 mL of dichloromethane and concentrated onto 1 g of silica gel which was added to the top of a column of 50 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes yielded 0.158 g (62%) of **320**.





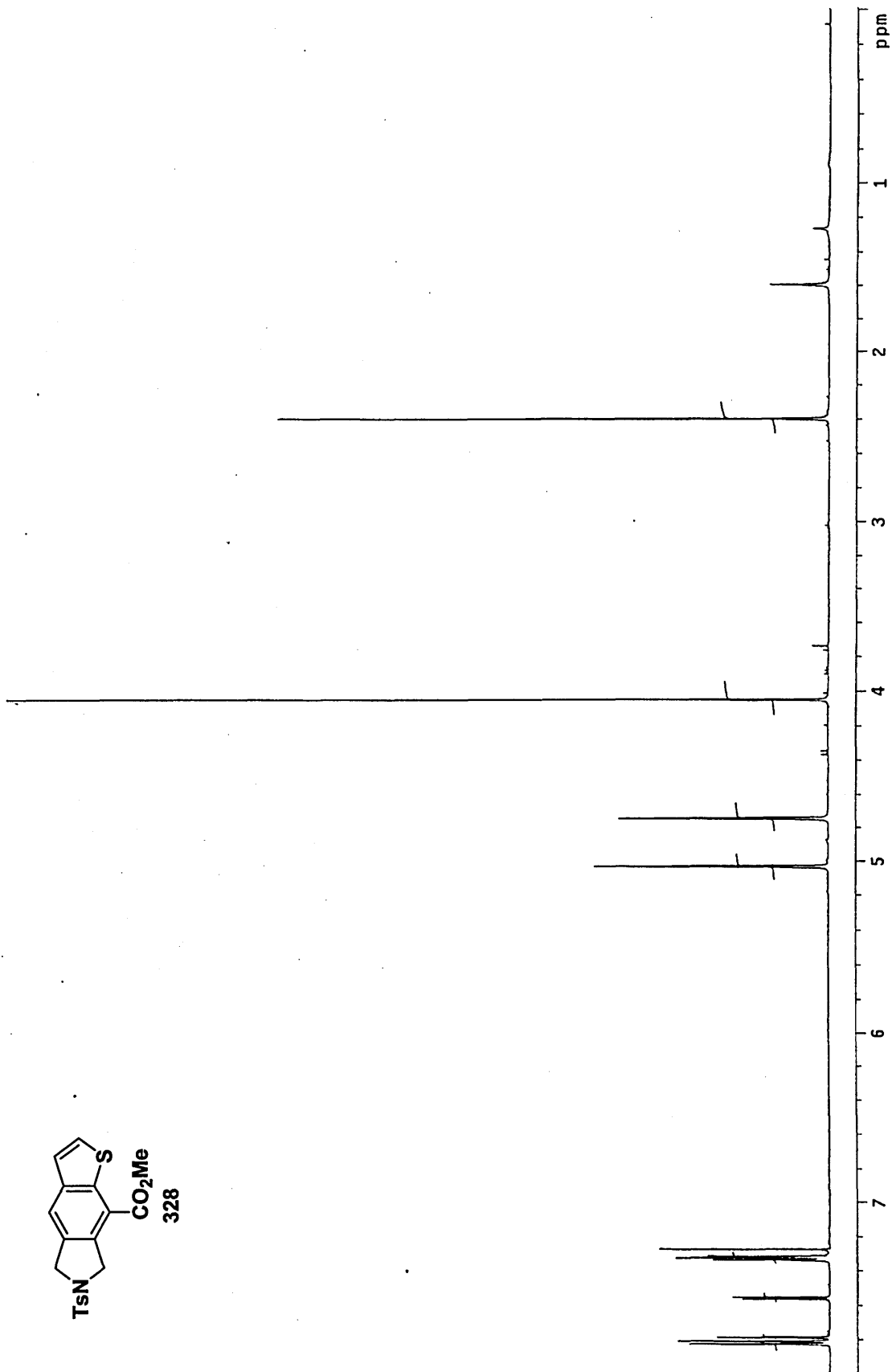
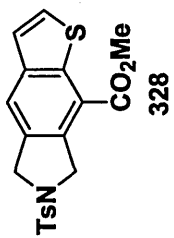
1-(*t*-Butoxycarbonyl)-4-formyl-5,6,7-trihydrocyclopenta[1,2-*f*]indole (327). A 50-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with alkynyl aldehyde **254** (0.458 g, 1.61 mmol), BHT (1.061 g, 4.817 mmol) and 30 mL of toluene. The reaction mixture was heated at reflux for 36 h, allowed to cool to room temperature, and then concentrated under reduced pressure to furnish 1.620 g of a dark-brown oil that was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 5 g of silica gel which was added to the top of a column of 150 g of silica gel. Gradient elution with 0-2% EtOAc-hexanes provided 0.235 g (51%) of **327** as a yellow solid: mp 89-92 °C; IR (thin film) 1728, 1688, 1602 and 1574 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.47 (s, 1 H), 8.29 (s, 1 H), 7.63 (d, *J* = 3.8 Hz, 1 H), 7.27 (dd, *J* = 3.8, 0.6 Hz, 1 H), 3.32 (t, *J* = 7.4 Hz, 2 H), 3.00 (t, *J* = 7.4 Hz, 2 H), 2.19 (quint, *J* = 7.4 Hz, 2 H), and 1.67 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 191.6, 149.6, 144.3, 142.3, 135.5, 128.5, 128.1, 117.2, 106.7, 84.1, 32.4, 30.6, 28.3 and 26.1; HRMS (*m/z*): [M+Na⁺] calcd for C₁₇H₁₉NO₃, 308.1257; found, 308.1266.

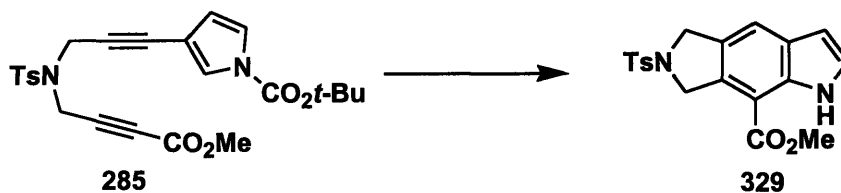




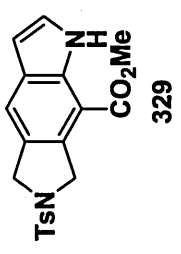
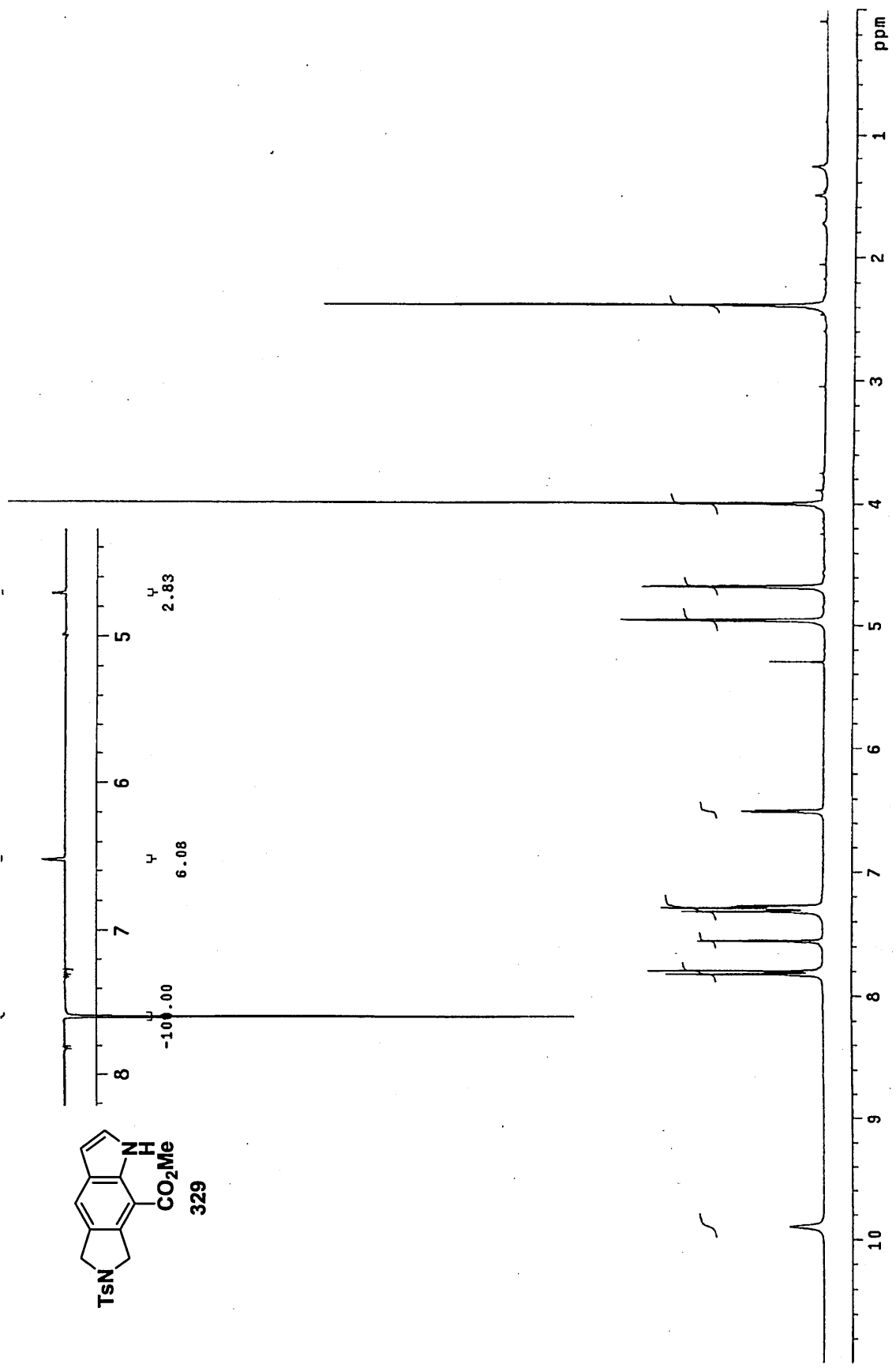
8-Carbomethoxy-6-[(4-methylphenyl)sulfonyl]thiopheno[3,2-f]isoindoline (328). A threaded Pyrex tube (ca. 25 mL capacity) was charged with alkynyl ester **290** (0.270 g, 0.697 mmol) and 14 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed under argon with a threaded teflon cap. The reaction mixture was heated in an oil bath at 150 °C for 3 h, allowed to cool to rt, transferred to a 50-mL round-bottomed flask with the aid of 20 mL of CH₂Cl₂, and concentrated under reduced pressure to furnish 0.289 g of a black oil. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 1 g of silica gel which was added to the top of a column of 20 g of silica gel. Gradient elution with 0-10% EtOAc-hexanes yielded 0.123 g (45%) of **328** as a light-brown solid: mp 222-224 °C; IR (thin film) 1709, 1597, and 1341 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (d, *J* = 8.4 Hz, 2 H), 7.78 (s, 1 H), 7.55 (d, *J* = 5.6 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 5.6 Hz, 1 H), 5.02 (s, 2 H), 4.74 (s, 2 H), 4.04 (s, 3 H), and 2.40 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 165.9, 143.8, 140.8, 140.4, 136.3, 134.1, 133.6, 130.1, 129.9, 127.6, 122.8, 121.8, 119.0, 55.3, 52.9, 52.8, and 21.8; HRMS (*m/z*): [M+Na⁺] calcd for C₁₉H₁₇NO₄S₂ 410.0491; found, 410.0483.

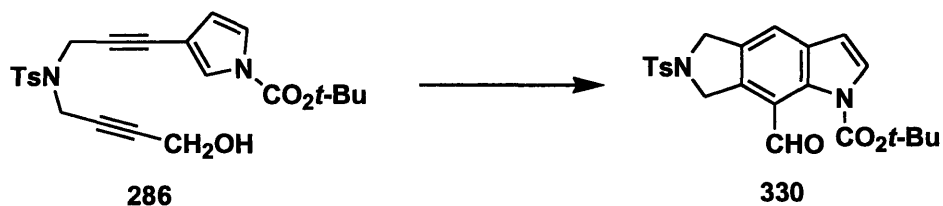
Lewis acid-catalyzed procedure: A 25-mL, round-bottomed fitted with a rubber septum and argon inlet needle was charged with alkynyl ester **290** (0.220 g, 0.568 mmol) and 12 mL of dichloromethane. The reaction mixture was cooled to 0 °C and 0.30 mL of Me₂AlCl solution (1.0 M in hexanes, 0.30 mmol) was added dropwise over 1 min. The reaction mixture was stirred at rt for 22 h, and then diluted with 20 mL of saturated aq NaHCO₃ solution and 50 mL of ether. The aqueous phase was separated and extracted with three 20-mL portions of ether, and the combined organic phases were dried over MgSO₄, filtered, and concentrated to provide yielded 0.216 g (98%) of pure **328**.



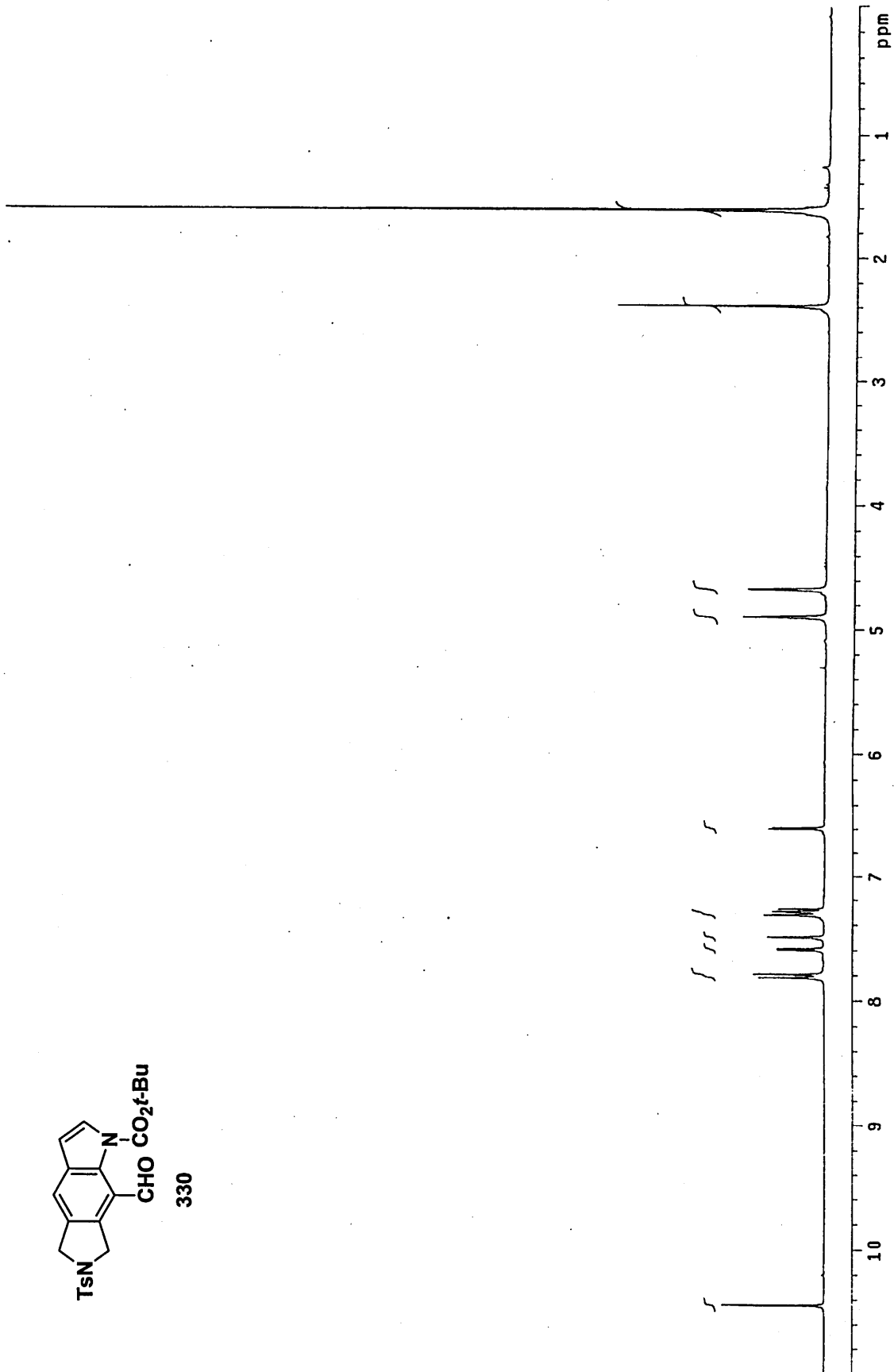
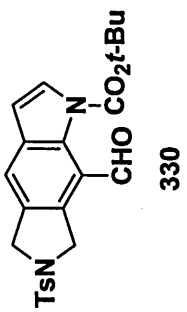


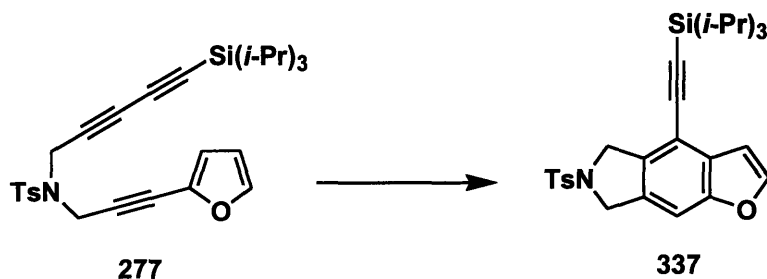
8-Carbomethoxy-6-[(4-Methylphenyl)sulfonyl]-3-pyrrolino[3,4-f]indole (329). A threaded Pyrex tube (ca. 25 mL capacity) was charged with alkynyl ester **285** (0.355 g, 0.755 mmol) and 15 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed under argon with a threaded teflon cap. The reaction mixture was heated in an oil bath at 160 °C for 16 h, allowed to cool to rt, transferred to a 50-mL round-bottomed flask with the aid of 20 mL of CH₂Cl₂, and concentrated under reduced pressure to furnish 0.293 g of a black oil. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 1 g of silica gel which was added to the top of a column of 20 g of silica gel. Gradient elution with 0-30% EtOAc-hexanes yielded 0.160 g (57%) of **329** as a light-yellow solid: mp 198-200 °C; IR (thin film) 3372, 1692, 1597, 1583 and 1164 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.90 (s, 1 H), 7.80 (d, *J* = 8.2 Hz, 2 H), 7.56 (s, 1 H), 7.38-7.24 (m, 3 H), 6.50 (dd, *J* = 3.3, 2.2 Hz, 1 H), 4.96 (s, 2 H), 4.68 (s, 2 H), 4.00 (s, 3 H), and 2.38 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 167.3, 143.7, 136.0, 133.9, 133.4, 130.0, 129.5, 128.5, 127.8, 126.2, 119.8, 107.6, 102.4, 55.2, 53.0, 52.3, and 21.7; HRMS (*m/z*): [M+Na⁺] calcd for C₁₉H₁₈N₂O₄S 393.0879; found, 393.0874.



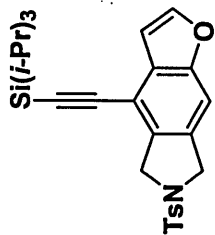


1-(*t*-Butoxycarbonyl)-8-formyl-6-[(4-methylphenyl)sulfonyl]-3-pyrrolino[3,4-*f*]indole (330). A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with alcohol **286** (0.267 g, 0.604 mmol), 12 mL of CH₂Cl₂, and Dess-Martin periodinane (0.384 g, 0.905 mmol). The reaction mixture was heated at reflux for 27 h, allowed to cool to room temperature, and then was filtered through 15 g of silica gel in a sintered glass funnel washing with 100 mL of 30% EtOAc-hexanes. The filtrate was concentrated under reduced pressure and diluted with 30 mL of aq 5% NaOH solution and 60 mL of CH₂Cl₂. The organic phase was separated and washed with 30 mL of water and the combined aqueous phases were extracted with two 50-mL portions of CH₂Cl₂. The combined organic phases were then washed with 50 mL of brine, dried over MgSO₄, filtered, and concentrated to furnish 0.240 g of a light-yellow solid that was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 1 g of silica gel which was added to the top of a column of 20 g of silica gel. Gradient elution with 0-50% EtOAc-hexanes provided 0.210 g (79%) of **330** as an off-white solid: mp 165-168 °C; IR (film) 1734, 1687, 1596, 1541, and 1347 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.45 (s, 1 H), 7.81 (d, *J* = 8.2 Hz, 2 H), 7.59 (d, *J* = 3.8 Hz, 1 H), 7.50 (s, 1 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 6.59 (d, *J* = 3.8 Hz, 1 H), 4.90 (s, 2 H), 4.67 (s, 2 H), 2.39 (s, 3 H), and 1.62 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 189.9, 150.4, 143.9, 134.6, 133.8, 133.7, 132.9, 132.7, 130.1, 129.2, 127.9, 119.4, 119.2, 108.1, 85.7, 54.8, 52.8, 28.1, and 21.7; HRMS (*m/z*): [M+Na⁺] calcd for C₂₃H₂₄N₂O₅S 463.1298; found, 463.1300.

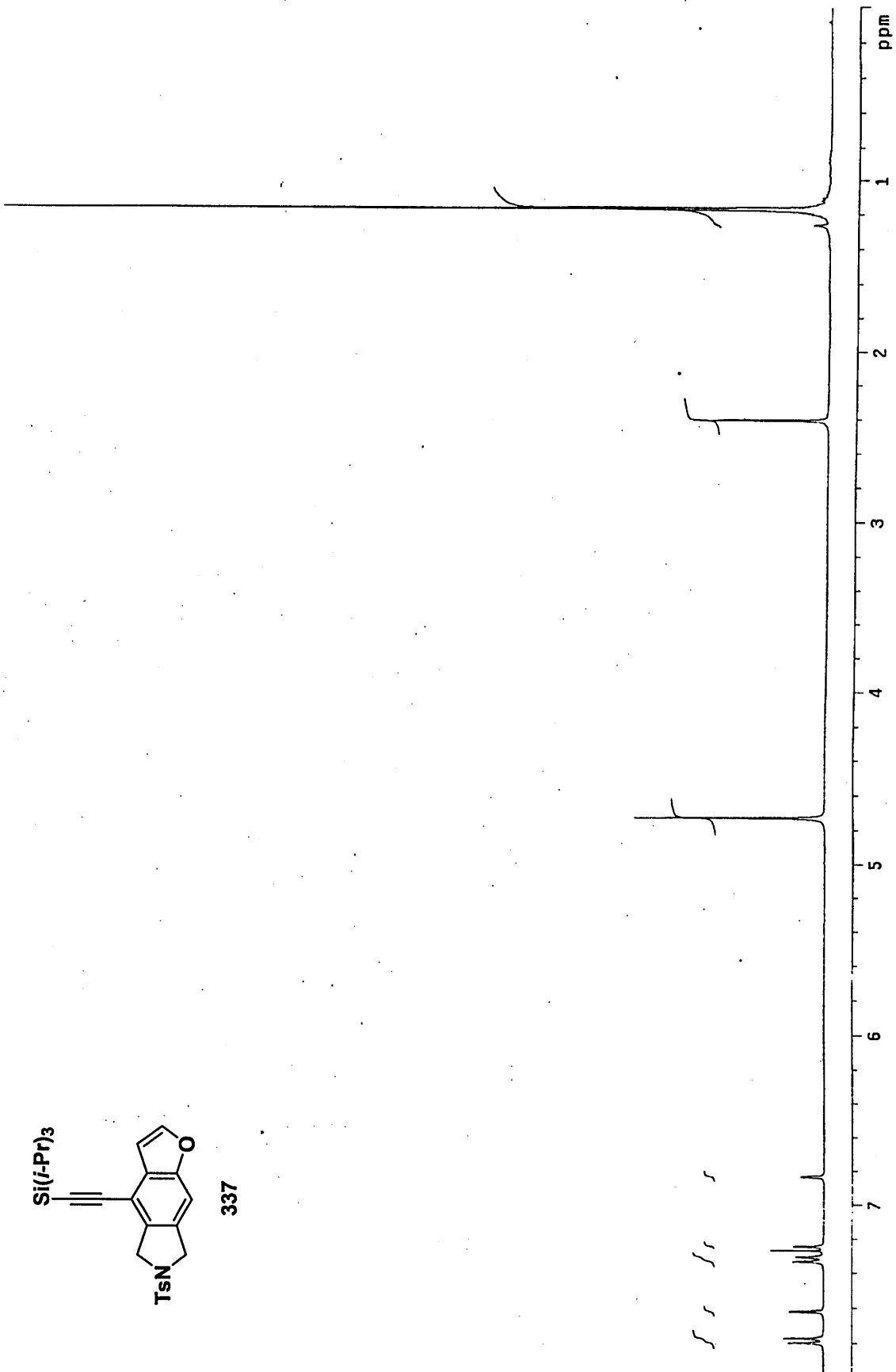


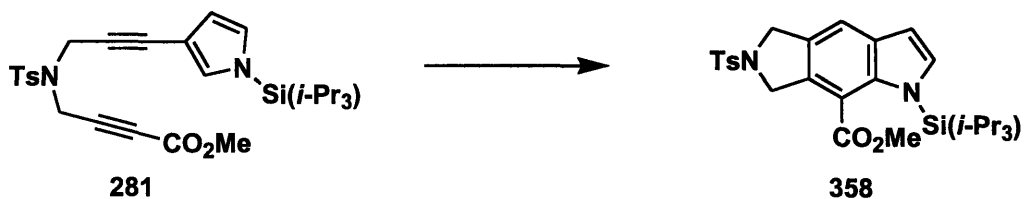


6-[(4-Methylphenyl)sulfonyl]-4-[(triisopropylsilyl)ethynyl]furano-[3,2-f]isoindoline (337). A 10-mL, pear-shaped flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with diyne **277** (0.059 g, 0.118 mmol), BHT (0.078 g, 0.36 mmol) and 2.4 mL of benzene. The reaction mixture was heated at reflux for 4 h, allowed to cool to room temperature, and then concentrated under reduced pressure to furnish 0.135 g of a dark-red semi-solid that was dissolved in 5 mL of CH₂Cl₂ and concentrated onto 0.3 g of silica gel which was added to the top of a column of 10 g of silica gel. Gradient elution with 0-2% EtOAc-hexanes provided 0.043 g (74%) of **337** as a dark-red viscous oil: IR (thin film) 2152, 1599, and 1348 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, *J* = 8.3 Hz, 2 H), 7.62 (d, *J* = 2.2 Hz, 1 H), 7.32 (d, *J* = 8.3 Hz, 2 H), 7.24 (d, *J* = 0.8 Hz, 1 H), 6.83 (dd, *J* = 2.2, 0.8 Hz, 1 H), 4.73 (s, 4 H), 2.40 (s, 3 H), and 1.26-1.08 (m, 21 H); ¹³C NMR (75 MHz, CDCl₃) δ 154.7, 146.4, 144.0, 134.3, 133.7, 132.8, 130.0, 129.7, 127.8, 110.8, 106.4, 106.3, 101.3, 99.4, 54.2, 53.5, 21.7, 18.9 and 11.4; HRMS (*m/z*): [M+Na⁺] calcd for C₂₈H₃₅NO₃SSi 516.1999; found, 516.1999.

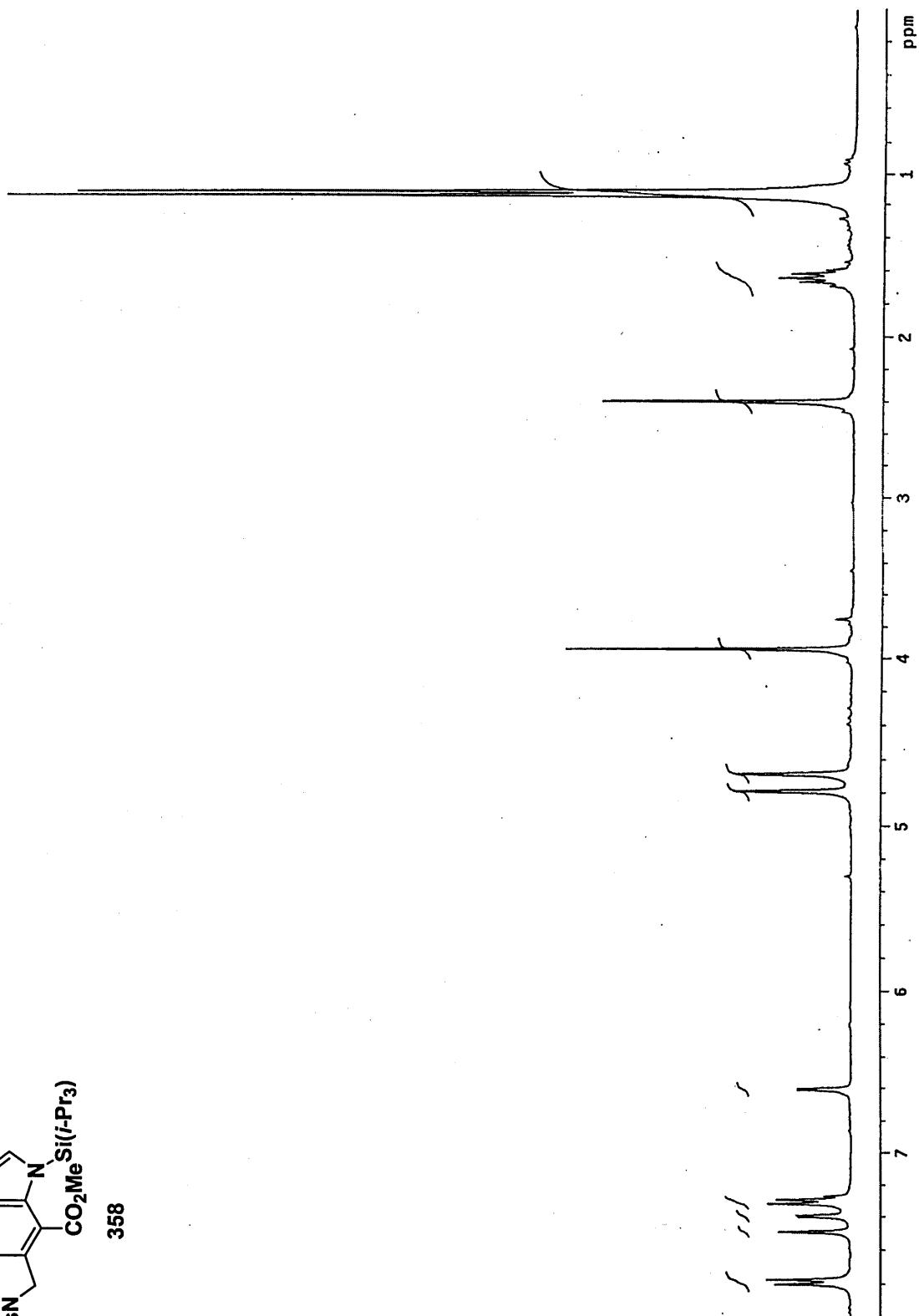
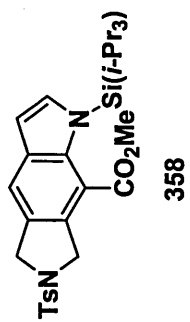


337





1-(Triisopropylsilyl)-8-carbomethoxy-6-[(4-methylphenyl)sulfonyl]-3-pyrrolo[3,4-f]indole (358). A threaded Pyrex tube (ca. 25 mL capacity) was charged with alkynyl ester **281** (0.215 g, 0.408 mmol) and 8 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed under argon with a threaded teflon cap. The reaction mixture was heated in an oil bath at 120 °C for 14 h, allowed to cool to rt, transferred to a 50-mL round-bottomed flask with the aid of 20 mL of CH₂Cl₂, and concentrated under reduced pressure to furnish 0.229 g of a black oil. This material was dissolved in 30 mL of CH₂Cl₂ and concentrated onto 2 g of silica gel which was added to the top of a column of 20 g of silica gel. Gradient elution with 0-10% EtOAc-hexanes yielded 0.081 g (37%) of **358** as a light-yellow paste: IR (thin film) 1722, 1597, and 1165 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.79 (d, *J* = 8.0 Hz, 2 H), 7.49 (s, 1 H), 7.40 (d, *J* = 3.3 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 6.61 (d, *J* = 3.3 Hz, 1 H), 4.79 (s, 2 H), 4.69 (s, 2 H), 3.94 (s, 3 H), 2.40 (s, 3 H), 1.65 (sept, *J* = 7.4 Hz, 3 H), and 1.13 (d, *J* = 7.4 Hz, 18 H); ¹³C NMR (75 MHz, CDCl₃) δ 168.8, 144.3, 138.7, 135.4, 134.4, 131.6, 130.5, 128.9, 128.4, 128.3, 118.3, 115.0, 105.5, 55.2, 53.8, 52.9, 22.2, 19.4, and 14.8.



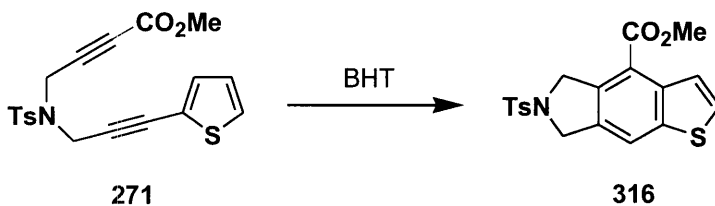
KINETICS DATA

All values for starting material (SM) and product (P) represent NMR integrations. At time zero, the reference peak followed throughout the experiment (either one or both methylenes within the tether) was set to the theoretical value of 2.00 (or 4.00 when they overlapped) and this allowed the determination of the relative integral of the internal standard. All subsequent integrations of the reference peak were determined by setting the integral of the internal standard to the value determined at time zero and extracting the relative value from the computer. Microsoft Excel was used for manipulating and plotting the data.

I. Various 4π components with an alkynyl ester as the 2π component

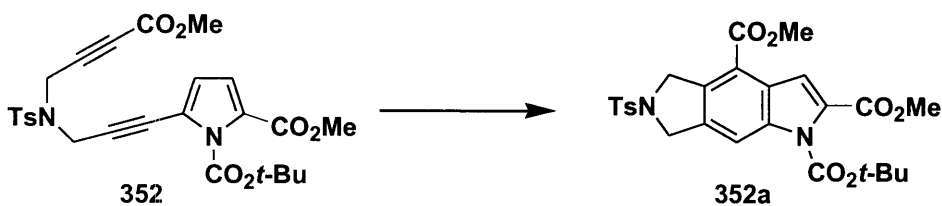


		271				316				
time (h)	SM1	SM2	SM3	AVG SM	%SM	ln(%SM)	k	t1/2 (h)		
0	2.00	2.00	2.00	2.00	100	4.61	0.0414	17		
1.5	1.87	1.92	1.89	1.89	95	4.55				
3	1.75	1.75	1.74	1.75	87	4.47				
5	1.52	1.54	1.53	1.53	76	4.34				
7	1.40	1.42	1.41	1.41	71	4.26				
10	1.28	1.26	1.28	1.27	64	4.15				
25	0.61	0.66	0.68	0.65	33	3.48				
32	0.57	0.59	0.61	0.59	30	3.38				
time (h)	P1	P2	P3	AVG P	%P	ln(%P)			k	t1/2 (h)
0	0.00	0.00	0.00	0.00	0	-			0.0317	22
1.5	0.23	0.27	0.29	0.26	13	2.57				
3	0.34	0.34	0.31	0.33	17	2.81				
5	0.42	0.39	0.43	0.41	21	3.03				
7	0.46	0.49	0.48	0.48	24	3.17				
10	0.51	0.50	0.53	0.51	26	3.25				
25	0.69	0.75	0.77	0.73	37	3.60				
32	0.76	0.81	0.80	0.79	40	3.68				



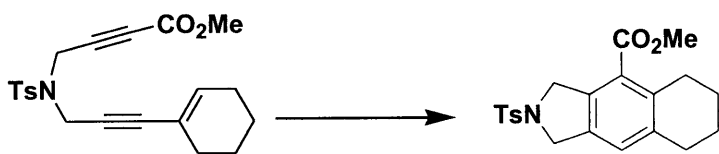
time (h)	SM1	SM2	SM3	AVG SM	%SM	ln(%SM)	k	t1/2 (h)
0	2.00	2.00	2.00	2.00	100	4.61	0.0474	15
1.5	1.71	1.78	1.79	1.76	88	4.48		
3	1.64	1.65	1.64	1.64	82	4.41		
5	1.50	1.50	1.49	1.50	75	4.32		
7	1.34	1.33	1.33	1.33	67	4.20		
10	1.18	1.18	1.19	1.18	59	4.08		
25	0.57	0.58	0.54	0.56	28	3.34		
32	0.48	0.49	0.51	0.49	25	3.21		

time (h)	P1	P2	P3	AVG P	%P	ln(%P)	k	t1/2 (h)
0	0.00	0.00	0.00	0.00	0	-	0.0359	19
1.5	0.24	0.27	0.28	0.26	13	2.57		
3	0.29	0.32	0.31	0.31	15	2.73		
5	0.34	0.42	0.36	0.37	19	2.92		
7	0.45	0.48	0.47	0.47	23	3.15		
10	0.52	0.50	0.52	0.51	26	3.24		
25	0.79	0.80	0.79	0.79	40	3.68		
32	0.83	0.83	0.84	0.83	42	3.73		



time (h)	SM1	SM2	SM3	AVG SM	%SM	ln(%SM)	k	t1/2 (h)
0.00	4.00	4.00	4.00	4.00	100	4.61	0.0235	29
10.00	3.05	3.05	3.05	3.05	76	4.33		
25.00	2.14	2.16	2.15	2.15	54	3.98		
31.00	1.51	1.53	1.52	1.52	38	3.64		
56.00	1.26	1.25	1.25	1.25	31	3.44		

time (h)	P1	P2	P3	AVG P	%P	ln(%P)	k	t1/2 (h)
0.00	-	-	-	-	-	-	0.0233	30
10.00	0.28	0.30	0.29	0.29	15	2.67		
25.00	0.72	0.77	0.74	0.74	37	3.62		
31.00	0.70	0.73	0.72	0.72	36	3.58		
56.00	0.95	0.96	0.95	0.95	48	3.86		

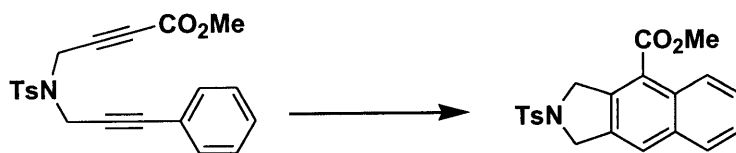


353

353a

time (h)	SM1	SM2	SM3	AVG SM	%SM	ln(%SM)	k	t1/2 (h)
0.00	4.00	4.00	4.00	4.00	100	4.6	0.1116	6
2.00	2.62	2.61	2.61	2.61	65	4.2		
3.67	1.87	1.87	1.87	1.87	47	3.8		
6.00	1.31	1.31	1.31	1.31	33	3.5		
9.50	0.91	0.90	0.89	0.90	22	3.1		
23.00	0.44	0.45	0.45	0.44	11	2.4		

time (h)	P1	P2	P3	AVG P	%P	ln(%P)	k	t1/2 (h)
0.00	0.00	0.00	0.00	0.00	0	-	0.0405	17
2.00	0.28	0.28	0.28	0.28	14	2.6		
3.67	1.87	0.45	0.45	0.46	23	3.1		
6.00	0.61	0.61	0.61	0.61	30	3.4		
9.50	0.73	0.73	0.73	0.73	36	3.6		
23.00	0.83	0.84	0.83	0.83	42	3.7		



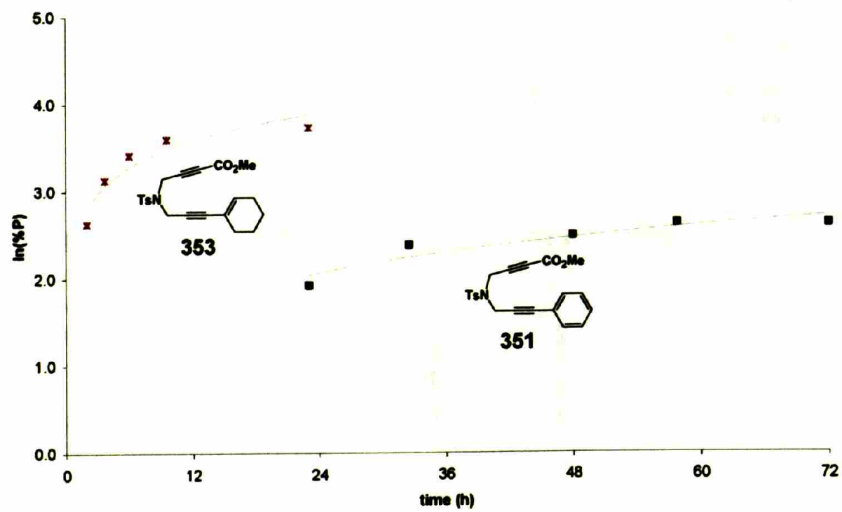
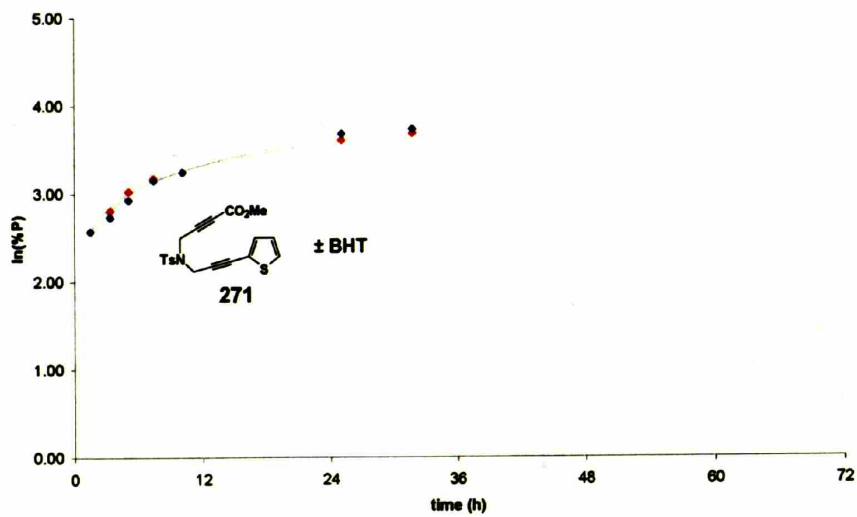
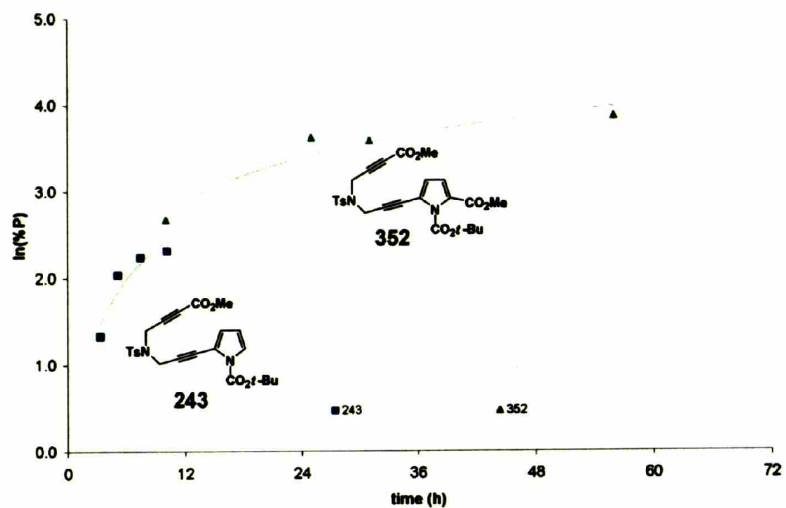
351

351a

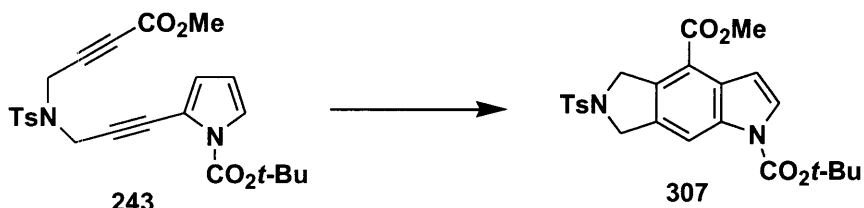
time (h)	SM1	SM2	SM3	AVG SM	%SM	ln(%SM)	k	t1/2
0.00	4.00	4.00	4.00	4.00	100	5	0.0022	315
6.00	3.83	3.82	3.84	3.83	96	5		
23.00	3.78	3.78	3.79	3.78	95	5		
32.50	3.72	3.71	3.72	3.72	93	5		
48.00	3.66	3.64	3.65	3.65	91	5		
57.75	3.60	3.57	3.54	3.57	89	4		
72.00	3.38	3.36	3.37	3.37	84	4		

time (h)	P1	P2	P3	AVG P	%P	ln(%P)	k	t1/2
0.00	0.00	0.00	0.00	0.00	0	-	0.0129	54
6.00	0.00	0.00	0.00	0.00	0	-		
23.00	0.14	0.14	0.14	0.14	7	2		
32.50	0.22	0.22	0.21	0.22	11	2		
48.00	0.25	0.24	0.24	0.24	12	2		
57.75	0.27	0.28	0.28	0.28	14	3		
72.00	0.27	0.27	0.28	0.27	14	3		

Appearance of Product – Alkynyl Esters with Different 4π Components

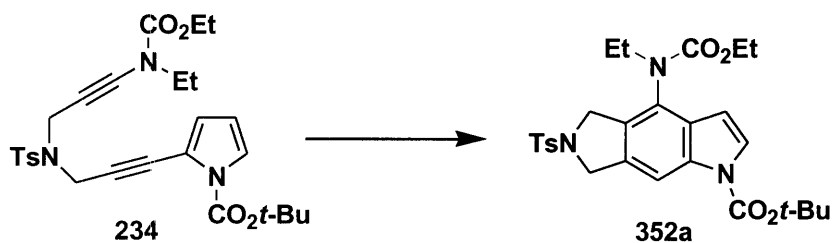


II. Alkynyl pyrrole 4π component with various 2π components



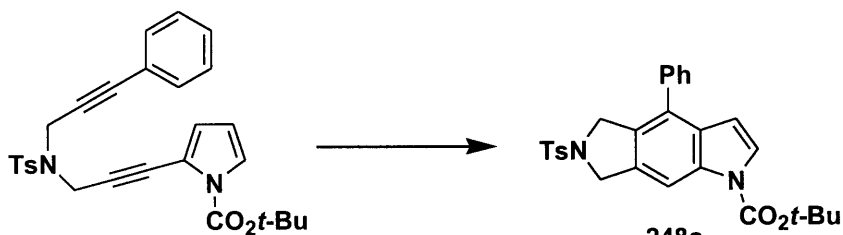
time (h)	SM1	SM2	SM3	AVG SM	%SM	ln(%SM)	k	t1/2 (h)
0.0	4.0	4.0	4.0	4.0	100	4.6	0.2351	3
1.5	3.0	3.0	3.0	3.0	75	4.3		
3.3	1.9	1.9	1.8	1.9	46	3.8		
5.1	1.1	1.1	1.1	1.1	27	3.3		
7.4	0.7	0.7	0.7	0.7	17	2.8		
10.1	0.4	0.4	0.4	0.4	10	2.3		

time (h)	P1	P2	P3	AVG P	%P	ln(%P)	k	t1/2 (h)
0.0	0.0	0.0	0.0	0.0	0.0	-	0.1327	5
3.3	0.1	0.2	0.2	0.2	3.8	1.3		
5.1	0.3	0.3	0.3	0.3	7.7	2.0		
7.4	0.4	0.4	0.4	0.4	9.4	2.2		
10.1	0.4	0.4	0.4	0.4	10.1	2.3		



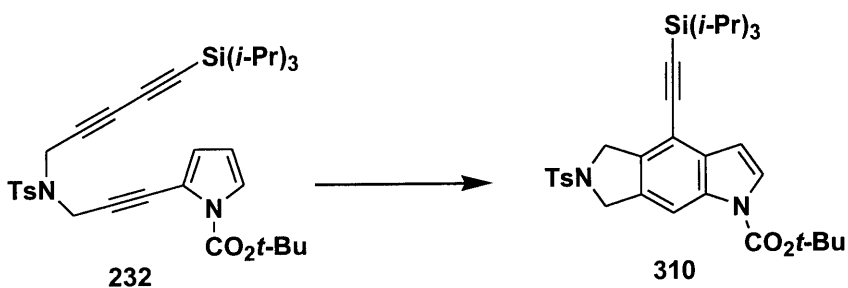
time (h)	SM1	SM2	SM3	AVG SM	%SM	ln(%SM)	k	t1/2 (h)
0.0	4.00	4.00	4.00	4.00	100	4.6	0.4183	2
1.2	2.78	2.78	2.78	2.78	70	4.2		
6.0	0.32	0.32	0.31	0.32	8	2.1		
8.0	0.00	0.00	0.00	0.00	0			

time (h)	P1	P2	P3	AVG P	%P	ln(%P)	k	t1/2 (h)
0.0	0.00	0.00	0.00	0.00	0	-	0.5575	1
1.2	0.04	0.04	0.04	0.04	1	0.0		
6.0	1.10	1.10	1.10	1.10	28	3.3		
8.0	1.40	1.39	1.40	1.40	35	3.6		



time (h)	248			AVG SM	% SM	ln(% SM)	k	t1/2 (h)
	SM1	SM2	SM3					
0.00	4.00	4.00	4.00	4.00	100	4.6	0.059	12
2.00	3.61	3.61	3.59	3.60	90	4.5		
6.00	3.06	3.05	3.05	3.06	76	4.3		
9.50	2.74	2.71	2.71	2.72	68	4.2		
23.00	1.31	1.27	1.27	1.28	32	3.5		
29.00	0.93	0.93	0.93	0.93	23	3.1		
32.50	0.74	0.74	0.74	0.74	19	2.9		
48.00	0.15	0.15	0.15	0.15	4	1.3		

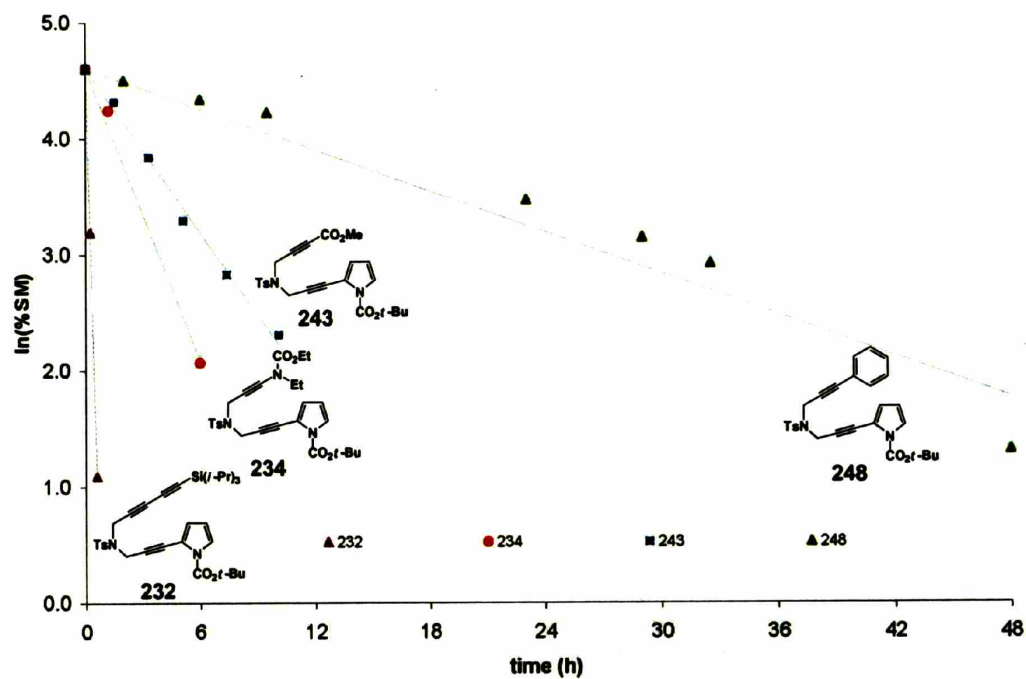
time (h)	P			AVG P	% P	ln(%P)	k	t1/2 (h)
	P1	P2	P3					
0.00	0.00	0.00	0.00	0.00	0.00	-	0.0455	15
2.00	0.04	0.04	0.04	0.04	2.03	0.71		
6.00	0.12	0.12	0.13	0.12	6.20	1.82		
9.50	0.22	0.22	0.23	0.22	11.17	2.41		
23.00	0.38	0.37	0.37	0.37	18.58	2.92		
29.00	0.41	0.41	0.41	0.41	20.52	3.02		
32.50	0.39	0.41	0.40	0.40	19.95	2.99		
48.00	0.49	0.49	0.49	0.49	24.45	3.20		



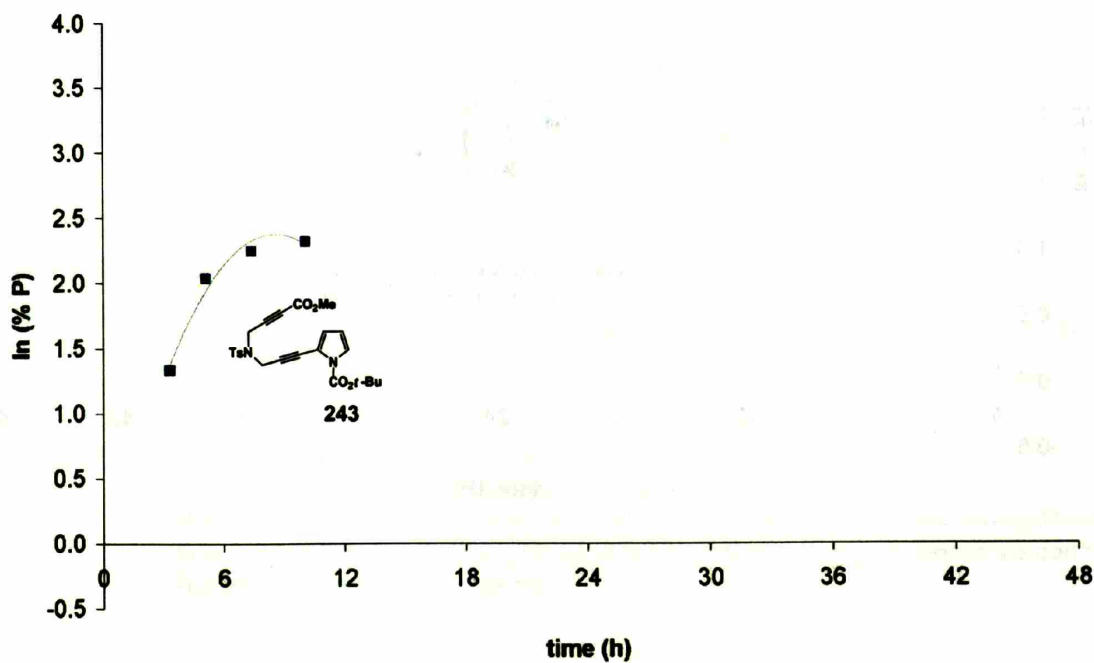
time (h)	SM			AVG SM	% SM	ln(% SM)	k	t1/2 (h)
	SM1	SM2	SM3					
0.0	4.00	4.00	4.00	4.00	100	4.6	5.9958	0.12
0.3	0.97	0.98	0.98	0.97	24	3.2		
0.6	0.13	0.11	0.12	0.12	3	1.1		

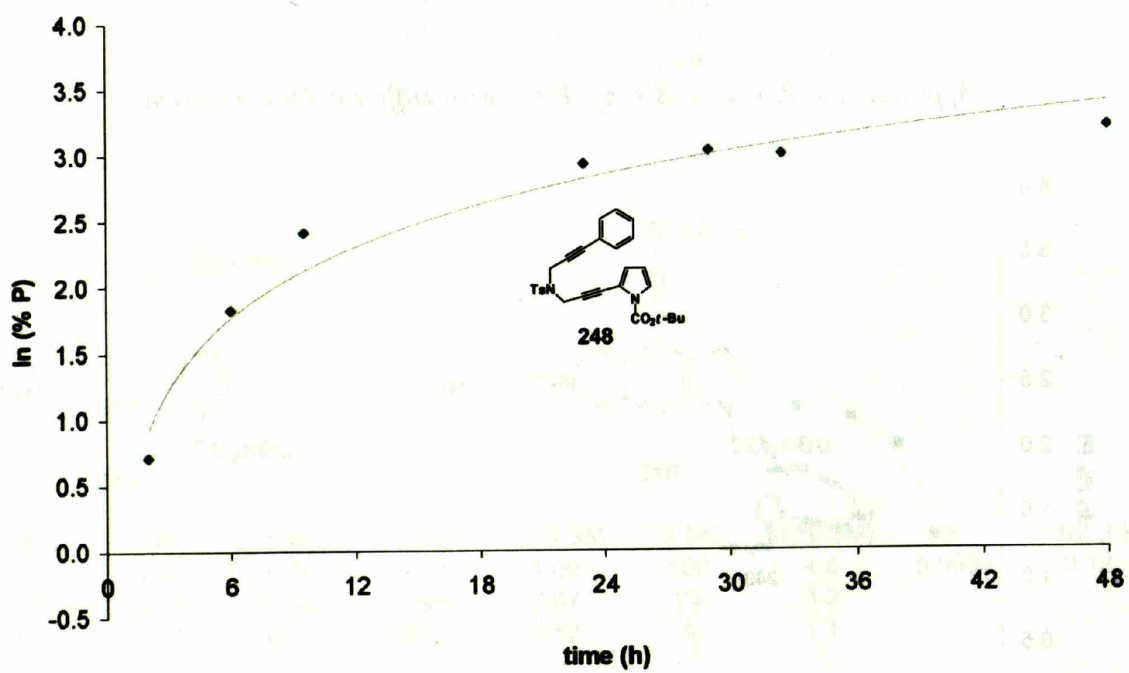
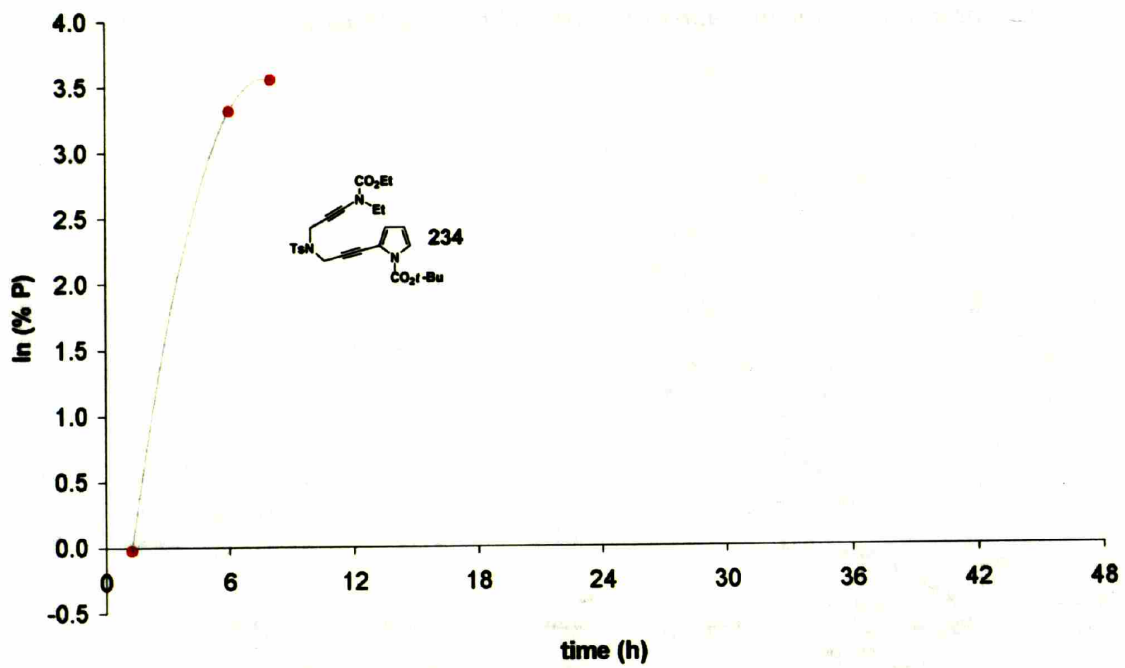
time (h)	P			AVG P	%P	lnP
	P1	P2	P3			
0.0	4.06	4.06	4.06	4.06	102	4.6
0.3	3.66	3.66	3.66	3.66	91	4.52
0.6	3.47	3.50	3.48	3.48	87	4.47

Disappearance of Starting Material – Alkynyl Esters with Different 2π Components



Appearance of Product – Alkynyl Esters with Different 2π Components





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OBJECTIVES

- To pursue a career that integrates the various aspects of my background and training. The ultimate goal is to have active interdisciplinary participation and oversight in a variety of areas by working at the interface between chemistry, biology, and medicine.

EDUCATION AND TRAINING

- 09.2001 - 05.2006 • **Ph.D. in Organic Chemistry**
Massachusetts Institute of Technology, Cambridge, MA • Research Advisor: Rick L. Danheiser
- 07.2000 - 06.2001 • **Resident in Internal Medicine**
Saint Vincent's Catholic Medical Center and New York Medical College, Staten Island, NY
Responsible for the direct care of hospitalized and ambulatory patients, participating in the treatment decision-making process at all levels. Daily lectures and case reports covering multiple areas of Internal Medicine complemented the hospital and clinic duties. *Supervisor: Susan Grossman, M.D.*
- 09.1996 - 05.2000 • **M.D.**
University of Miami School of Medicine and Jackson Memorial Medical Center, Miami, Florida
- 09.1993 - 06.1996 • **M.M.Sc.**
Harvard University and Harvard Medical School, Boston, MA
Graduate student in Immunology Program of the Division of Medical Sciences and the Harvard-Markey Biomedical Scientist Program. Completed many courses at graduate and medical school levels, including all course requirements for the Immunology Ph.D. degree.
- 08.1992 - 05.1993 • **University of Puerto Rico at Mayagüez, Mayagüez, PR**
Graduate student, instructor and researcher in the Department of Chemistry. Completed most of the course requirements for the M.S. degree in Chemistry while doing research and teaching. *Research Advisor: René S. Vieta*
- 08.1987 - 06.1992 • **B.S. in Chemistry, Magna Cum Laude, (GPA 4.00)**
University of Puerto Rico at Mayagüez, Mayagüez, PR
After completing the course requirements for the B.S. in Chemistry in 1991, enrolled for an additional year as an undergraduate to undertake further coursework in chemistry, biology, mathematics and art history. Also performed research in biochemistry.
- Summer 1990 • **Undergraduate Research Fellow**
Eastman Kodak Research Laboratories, Rochester, NY
Performed research in the development of new methods for the preparation of photographic coupler dispersions.

HONORS AND AWARDS

- 05.2005 • **Wyeth Scholar**
Award recognizing outstanding accomplishments in research and the excellence of a lecture presented at the 2005 Graduate Research Symposium in Organic and Bioorganic Chemistry at MIT. Funding to attend a professional conference by Wyeth Research was provided as part of the award.
- 05.2005 • **2005 Excellence in Teaching Award**
Award recognizing excellence in teaching undergraduates at MIT.
- 09.1994 - 06.1996 • **NIH Minority Predoctoral Fellowship**
Award for funding of graduate studies granted after submission of an original proposal.
- 06.1992 • **Luis Stéfani Rafucci Great Award**: Most outstanding student of the University of Puerto Rico at Mayagüez, 1992 graduating class.
• **Arts and Sciences Faculty Award**: Most outstanding A&S student, University of Puerto Rico at Mayagüez, 1992 graduating class.
• **Antoine Lavoisier Award**, Most outstanding Chemistry student, University of Puerto Rico at Mayagüez, 1992 graduating class.
- 1988 - 1992 • Honor Student of the Arts and Sciences Faculty of the University of Puerto Rico at Mayagüez.

PUBLICATIONS

- Horta, J. E. and Danheiser, R. L. **Intramolecular [4+2] Cycloadditions of Heteroenynes and Alkynes. An Efficient Strategy for the Synthesis of Polycyclic Heteroaromatic Compounds.** *Manuscript in preparation, to be submitted to the Journal of Organic Chemistry.*

AFFILIATIONS AND LICENSURES

- Since 2005 • **Commonwealth of Puerto Rico Active Medical License**
- Since 2004 • **Commonwealth of Massachusetts Active Medical License**
- Since 1996 • **American Medical Association**
- Since 1990 • **National Honor Society Phi Kappa Phi**
- Since 1988 • **American Chemical Society**

LANGUAGES

- **Fluent in English and Spanish. Can read Italian and some French.**

REFERENCES

- ① **Rick L. Danheiser**, A. C. Cope Professor of Chemistry, Massachusetts Institute of Technology
- ② **Timothy M. Swager**, Chairman, Dept of Chemistry, Massachusetts Institute of Technology
- ③ **Barbara Imperiali**, Professor of Chemistry, Massachusetts Institute of Technology