SYNTHESIS OF 3-AMINOCYCLOBUTENONES VIA [2 + 2] CYCLOADDITION OF YNAMIDES AND KETENES

by

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We cannot seek achievement for ourselves and forget about progress and prosperity for our community... Our ambitions must be broad enough to include the aspirations and needs of others, for their sakes and for our own.
-Cesar Chavez

Only she who attempts the absurd can achieve the impossible.
-Robin Morgan

The opportunity to attend graduate school at MIT was an unexpected possibility that opened doors to unforeseen adventures in both my career and in my personal life. Growing up in a very small town, I never imagined my life would lead me here to a world-renowned university 3,000 miles away from home. Nor did I ever anticipate that the journey would be so long and arduous. It was, thus, through great sacrifice coupled with a tenacious spirit, and a cohort of phenomenal teachers and mentors that thesis was made possible.

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I became a zealous student with an insatiable desire for learning. I was fortunate to have some amazing teachers at Imperial Valley College, San Diego Mesa College, and the University of California, San Diego. I'd especially like to thank Professor Joe Archuleta (IVC) for never closing his office doors as he shepherded me through Physics (light and optics) and Calculus II.

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For Mom and Jerry

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ABSTRACT

Ynamides react with various classes of ketenes in intermolecular [2 + 2] cycloaddition to afford substituted cyclobutenones with complete regioselectivity. The cycloaddition substrates are easily assembled from amine derivatives by copper-catalyzed N-alkynylation with acetylenic bromides. The alkynylation reaction provides access to thermally sensitive compounds such as diynamides. Synthesis of the requisite halo diynes is achieved by Sonogashira coupling followed by base-mediated elimination at low temperature.

Thesis Supervisor: Rick L. Danheiser
Title: Professor of Chemistry

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Part I

Results and Discussion

Chapter 1

Synthesis of Ynamides via N-Alkynylation of Amine Derivatives

Strategies for Ynamide Synthesis

There are several methods available for the synthesis of the ynamides.[1] Galy[2] introduced one of the earliest strategies for the synthesis of ynamides: base-catalyzed isomerization of propargyl amides. This method was further developed by Katritzky,[3] Majumdar,[4] Hsung,[5] and Gravestock.[6] Another important strategy for the synthesis of ynamides involves the elimination of halo enamides. Studies by Viehe,[7] Zemlicka,[8] Brückner,[9] and Hsung[5] demonstrated various methods for the preparation of requisite halo enamides that are converted to ynamides upon treatment with base. Saa later reported significant improvements on the dehalogenation of halo enamides.[10]

The addition of metalated amides to alkynyl(phenyl)iodonium salts is also a useful strategy for the synthesis of ynamides.[11] While alkynyl(phenyl)iodonium salts are versatile

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[1] DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064.
[2] (a) Galy, G. P.; Elguero, J.; Vincent, E. J.; Galy, A. M.; Barbe, J. *Synthesis* **1979**, 944. (b) Mahamoud, A.; Galy, J. P.; Vincent, E. J.; Barbe, J. *Synthesis* **1981**, 917.
[3] Katritzky, A. R.; Ramer, W. H. *J. Org. Chem.* **1985**, *50*, 852.
[4] Majumdar, K. C.; Ghosh, S. K.; *Synth. Commun.* **1994**, *24*, 217.
[5] (a) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459. (b) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417.
[6] Gravestock, D.; Dovey, M. C. *Synthesis* **2003**, 523.
[7] Janousek, Z.; Collard, J.; Viehe, H. G. *Angew. Chem., Int. Ed Engl.* **1972**, *11*, 917.
[8] Joshi, R. V.; Xu, Z.-Q.; Ksebati, M. B.; Kessel, D.; Corbett, T. H.; Drach, J. C.; Zemlicka, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1089.
[9] (a) Brückner, D. *Synlett* **2000**, 1402. (b) Hoffmann, R. W.; Brückner, D. *New J. Chem.* **2001**, *25*, 369.
[10] (a) Rodriguez, D.; Castedo, L.; Saa, C. *Synlett* **2004**, 783. (b) Rodriguez, D.; Martinez-Esperon, M. F.; Castedo, L.; Saa, C. *Synlett* **2007**, 1963.
[11] For reviews of the synthesis and chemistry of alkyl(phenyl)iodonium salts, see: (a) Stang, P. J. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995; pp 67–98. (b) Zhdankin, V. V.;

reagents for organic synthesis, there are several limitations regarding the use of these compounds in alkynylation reactions. Harder nucleophiles directly attack the iodine and decompose the onium salt through non-alkynylation pathways.[12] In addition, alkynyl(phenyl)iodonium salts cannot provide ynamides with alkyl substituents on the acetylene. The addition of soft nucleophiles to alkynyl(phenyl)iodonium salts is believed to proceed via the rearrangement of an alkylidenecarbene intermediate which can undergo a 1,2-shift[11] only when the migrating substituent is a hydrogen atom, trialkylsilyl group, or aryl moiety and never with alkyl substituents.

Another strategy for ynamide synthesis is cross coupling amides with terminal or halo alkynes. Balsamo[13] serendipitously discovered this first example of the reaction of *t*-butyl propiolate with a β-lactam under aerobic conditions ($CuCl_2$, O_2, HMPA). The utility of this method was not realized until many years later. In 2002, we turned our attention to the synthesis of ynamides using the palladium and copper catalyst systems that were designed for the amidation of aryl halides by Buchwald.[14] Our initial results were disappointing, as the ynamide formation could not compete with the homocoupling of the halo acetylene.

We then examined protocols in which complete conversion of the amide substrate to its copper derivative was carried out prior to the addition of the alkynyl halide. We believed that pre-forming the copper amide would maximize the rate of its reaction with the halo acetylene and make the desired ynamide formation competitive with the homocoupling process.

Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (c) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927. (d) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (e) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274.

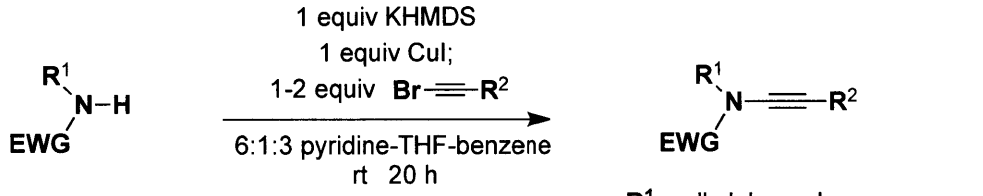
[12] For an example, see: Margida, A. J.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 4703.

[13] Balsamo, A.; Macchia, B.; Macchia, F.; Rossello, A.; Domiano, P. *Tetrahedron Lett.* **1985**, *26*, 4141.

[14] (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

We were encouraged by an analogous report by Ogawa[15] on the formation of enamides from preformed copper amides and alkenyl halides; however, the thermal conditions employed by Ogawa (130 °C) were unsuitable for the preparation of thermally sensitive ynamides. We were interested in developing a protocol using milder conditions and we found that our N-alkynylation reaction was successful at room temperature by treating amide derivatives with stoichiometric amounts of KHMDS and CuI before the addition of the alkynyl halide. These reactions proceed in the presence of pyridine and do not require additional ligands to activate the copper for the coupling reaction.[16]

A broad range of alkynyl bromides participate in the reaction, including compounds that are especially prone to homocoupling. Acyclic carbamates, sulfonamides, oxazolidinones, and cyclic ureas all undergo N-alkynylation in good yield. Significantly, the alkynylation reaction proceeds smoothly at room temperature, allowing its application to the synthesis of several classes of thermally sensitive ynamides, such as diynamides.



(1)

R^1 = alkyl, benzyl
R^2 = alkyl, alkenyl, aryl, silyl
EWG = CO_2Me, CO_2t-Bu, tosyl

During the course of our studies, Hsung and co-workers[17] reported an analogous method that employed a *catalytic* amount of copper (CuCN) with a mild base (K_3PO_4) at elevated

[15] Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443.
[16] Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011
[17] (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368. (b) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151.

temperatures (110 °C) that, unfortunately, lead to dimerization of certain alkynyl halides. Hsung later developed a second-generation catalyst system, employing copper sulfate and 1,10-phenanthroline, to address some of the limitations of his previous method. Hsung's new protocol suppresses the dimerization of alkynyl halides and improves the yields of N-alkynylation for several classes of amide derivatives such as sulfonamides, imidazolidinones, and acyclic carbamates that did not participate efficiently in the first-generation coupling reaction. However, Hsung's modified protocol still requires prolonged reaction times (18-36 h) and elevated temperatures (60-95 °C), which may be unsuitable for the preparation of thermally sensitive ynamides.

Tam and co-workers[18] reported another procedure for the copper-catalyzed alkynylation of acyclic carbamates that combines aspects our protocol with Hsung's second-generation protocol. Tam's method utilizes CuI (2-3 mol%) and 1,10-phenanthroline (2.2-3.6 mol%) in toluene with the slow addition of KHMDS over several hours at elevated temperature (90 °C), presumably to avoid formation of the unreactive diamido cuprate shown in Scheme 1.[14] We were concerned to find that Tam was unable to use our method to reproduce the yield for ynamide **1** from our recent publication (Table 1, entry 1). We investigated the effects of varying the quality of pyridine used in the preparation of ynamide **2** (Table 1, entry 2).

[18] Riddell, N.; Villenueve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681.

Scheme 1

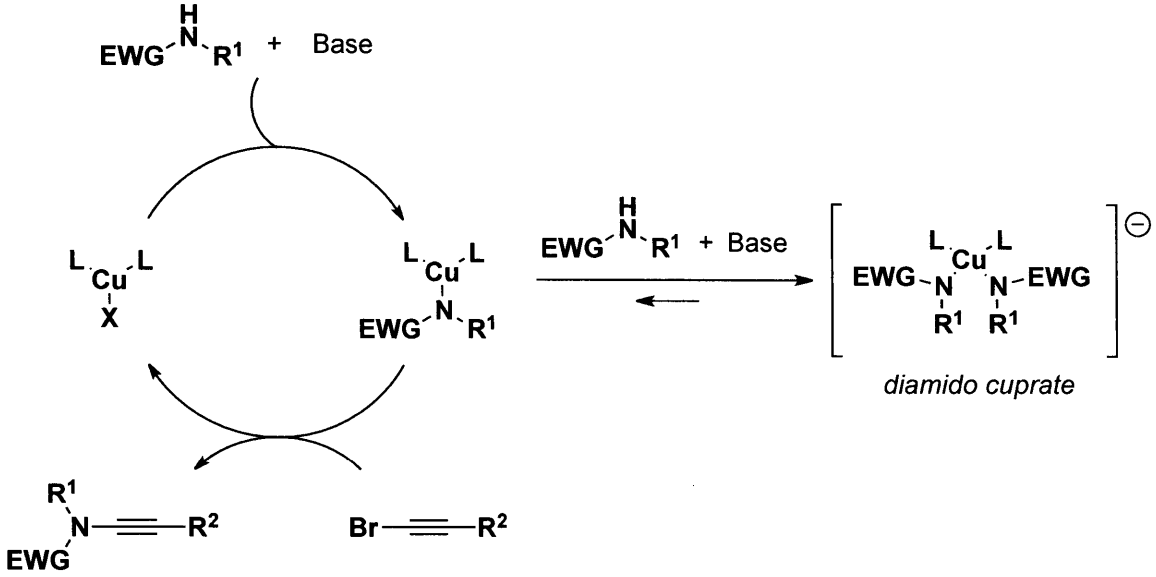
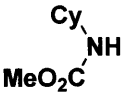
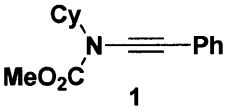
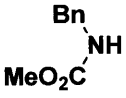
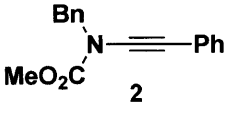


Table 1. Synthesis of Ynamides **1** and **2**

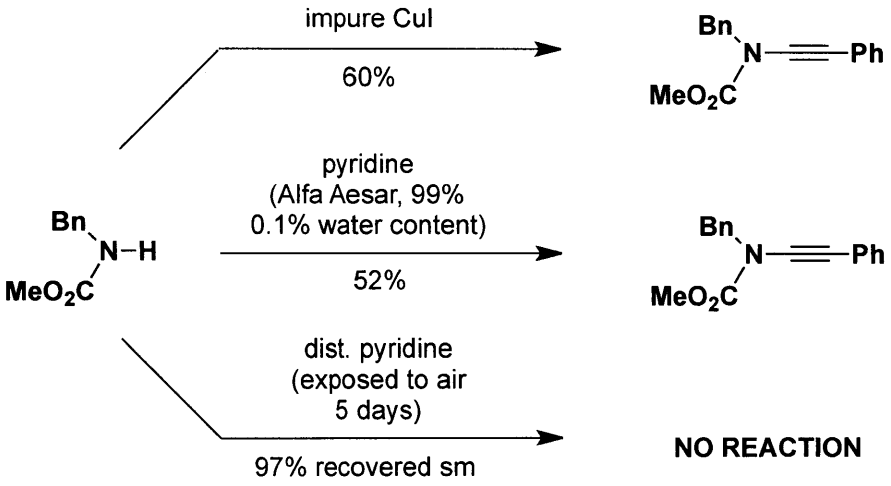
			% Yield[a]	
Entry	carbamate	ynamide	Tam	Danheiser
1		 **1**	16%	42%
2		 **2**	0%	63%

[a] Isolated yields of products purified by column chromatography.

The use of freshly distilled pyridine from CaH_2 afforded ynamide **2** in 63% yield whereas

Tam reports a yield of 0% for this ynamide. When pyridine is utilized from a freshly opened bottle (Alfa Aesar, 99%, 0.1% water content) the yield of ynamide **2** decreased to 52% (Scheme 2). In addition, we observed that no reaction occurred when using distilled pyridine that had been exposed to air for several days. As a result, we presume that the pyridine Tam used for our N-alkynylation method was either not freshly distilled or not properly stored which resulted in low yields of ynamide products.

Scheme 2



Synthesis of Diynamides

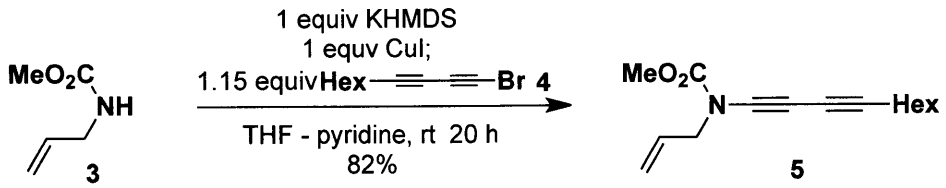
We became interested in investigating the reactivity of diynamides in benzannulation reactions for the synthesis of nitrogen heterocycles.[19] Diynamides were unknown until 2003 when they appeared in connection with the initial development of our N-alkynylation

[19] Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.* **2011**, *76*, 1852.

procedure.[16] One diynamide target of interest was compound **5**. Optimal reaction conditions for the synthesis of diynamide **5** were found by altering a number of variables such as solvent composition, reagent stoichiometry, and the work-up procedure.

Initially, the reaction was conducted in a 6:1:3 mixture of pyridine-THF-benzene. The new conditions only require 25 equivalents of pyridine with THF (1:7 pyridine-THF) as the reaction solvent. Stirring the reaction became problematic on scales exceeding 4 grams of the starting allyl carbamate (**3**) when employing concentrations higher than 0.2 M in THF. In such cases, it was essential to add the pyridine before the deprotonation step in order to increase the solubility of the deprotonated amide. It is important to note that while employing smaller amounts of pyridine lowers the yield of product, increasing the amount of pyridine does not significantly change the yield. Finally, to render the experimental procedure more "user-friendly", modifications were made in the mode of addition of CuI and the work-up procedure.

Though we used our N-alkynylation procedure to prepare this diynamide with no difficulty, preparation of the requisite bromo 1,3-diyne (**4**) proved unexpectedly challenging. This provided the impetus for our search for an efficient synthesis of 1,3-diynes.



(2)

Synthesis of 1,3-Diynes

Conjugated diynes have been widely exploited in the preparation of synthetic building

blocks for natural products,[20] electronic and optical materials,[21] and molecular receptors.[22] There are many synthetic routes to unsymmetrical 1,3-diynes. The most common route involves cross-coupling reactions that, unfortunately, are often plagued with competing side reactions such as Glaser-type homocoupling[23] and by the formation of mixtures of cross-coupling products that can be difficult to separate. The copper-catalyzed Cadiot-Chodkiewicz reaction,[24] developed in the late 1960s, is among the most widely used method for effecting unsymmetrical alkyne coupling. This method has been utilized in the synthesis of terminal diynes by deprotection of one end of the conjugated diyne generated from the Cadiot-Chodkiewicz reaction.[25] The protecting group is often a silyl moiety or a tertiary alcohol, which can be deprotected via base-promoted cleavage; however, in some cases this has led to isomerization of the terminal diyne to the more thermodynamically stable internal diyne.[26]

Since the development of the Sonogashira reaction,[27] palladium-catalyzed cross coupling has emerged as a powerful tool for the preparation of enynes that can be converted to both internal and terminal unsymmetrical diynes. This approach was used by Linstrumelle[28] as a

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[20] For some examples, see: (a) Sugahara, T.; Ogasawara, K. *Chem. Commun.* **1997**, 767. (b) Rossi, R.; Bellina, F.; Catanese, A.; Mannina, L.; Valensin, D. *Tetrahedron* **2000**, *56*, 479. (c) Saito, S.; Uchiyama, N.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, *4338*. (d) Jeevanandam, A.; Korivi, R. P.; Huang, I.; Cheng, C-H. *Org. Lett.* **2002**, *4*, 807. (e) Kirkham, J. E. D.; Courtney, T. D. L.; Lee, V.; Baldwin, J. E. *Tetrahedron* **2005**, *61*, 7219. For a review of natural products containing conjugated diynes, see; (h) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1.

[21] (a) Ginsburg, E. J.; Gorman, C. B.; Grubbs, R. H. In *Modern Acetylene Chemistry*; Stang, P. J., Diedrich, F., Eds.; VCH: Weinheim, 1995. (b) Camacho, D. H.; Saito, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 924. (c) Liao, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2003**, *5*, 909.

[22] Lee, L-H.; Lynch, V.; Lagow, R. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2805 and references therein.

[23] *Science of Synthesis: Houben Weyl Methods of Molecular Transformations*; Mller, E., Ed.; Thieme: Stuttgart, 1977; Vol. 5, 925-928.

[24] For reviews, see: (a) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969. (b) Siemsen, P.; Livingston, R. C.; Diedrich, F. *Angew. Chem., Int. Ed Engl.* **2000**, *39*, 2632.

[25] Zeni, G.; Panatieri, R. B.; Lissner, E.; Menezes, P. H.; Braga, A. L.; Stefani, H. *Org. Lett.* **2001**, *3*, 819.

[26] (a) Vereshchagin, L. I.; Buzilova, S. R.; Bol'shdvorskaya, R. L.; Kirillova, L. P. *J. Org. Chem. USSR (Engl. Transl.)* **1976**, *12*, 1174 and references therein. (b) Bumagin, N. A.; Ponomaryov, A. B.; Beletskaya, I. P. *Synthesis* **1984**, 728.

[27] Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874 and references therein.

[28] (a) Linstrumelle, G.; Ratovelomanana, V. *Tetrahedron Lett.* **1981**, *22*, 315. (b) Ratovelomanana, V.; Hammoud, A.; Linstrumelle, G. *Tetrahedron Lett.* **1987**, *28*, 1649. (c) Alami, M.; Crousse, B.; Linstrumelle, G. *Tetrahedron Lett.* **1995**, *36*, 3687

route to terminal 1,3-diynes by treating the intermediate chloro enynes with a strong base. Kende[29] reported the synthesis of various terminal 1,3-diynes by a similar two-step addition-elimination pathway using tetra-*n*-butylammonium fluoride for the dehydrohalogenation of chloro enynes. More recently, the Sonogashira reaction has been applied to the synthesis of internal conjugated diynes via direct cross coupling of halo alkynes with mono-protected terminal alkynes.[30] The internal diynes may be converted to the terminal diynes by mono-deprotection[9] or by prototopic isomerization via the acetylene zipper reaction.[31]

Fuchs and co-workers[32] developed a catalyst-free approach to the construction of 1,3-diynes. Their five-step synthesis involves treatment of benzaldehyde with the prepared 3,3,3-trichloropropyl-1-triphenylphosphorane in the presence of sodium hexamethyldisilazide to access the corresponding alkynyl chloride which is then subjected to base-mediated elimination to afford buta-1,3-diynylbenzene as the only example reported. In addition to Fuchs' method, the Fritsch-Buttenberg-Wiechell rearrangement[33] of lithiated derivatives of 1,1-dibromo enynes provides internal diynes as an alternative to metal-catalyzed cross coupling. The limitations of the method are two-fold: the number of steps (5) required to access a terminal diyne may not be convenient and this method is not applicable to the preparation of alkyl substituted diynes due to unproductive pathways of enolate formation during acetylide addition to the requisite aldehyde.

We first explored the synthesis of our target bromo 1,3-diyne **4** using strategies based on the Cadiot-Chodkiewicz reaction. For example, copper-mediated cross coupling of bromo

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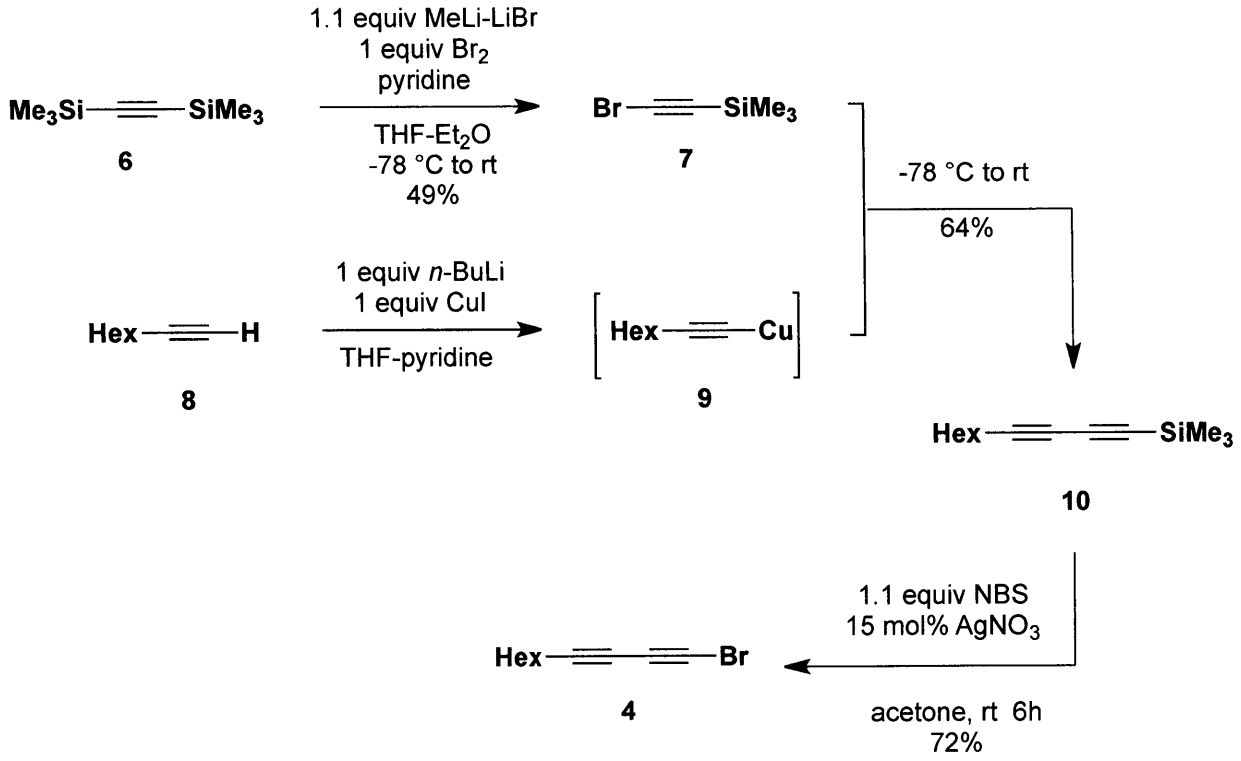
[29] Kende, A. S.; Smith, C. A. *J. Org. Chem.* **1988**, *53*, 2655.
[30] For some examples, see: (a) López, S.; Fernández-Trillo, F.; Castedo, L.; Saá, C. *Org. Lett.* **2003**, *5*, 3725. (b) Kim, S.; Kim, S.; Lee, T.; Ko, H.; Kim, D. *Org. Lett.* **2004**, *6*, 3601.
[31] Balova, I. A.; Morozkina, S. N.; Knight, D. W.; Vasilevsky, S. F. *Tetrahedron Lett.* **2003**, *44*, 107 and references therein.
[32] Karatholuvhu, M. S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2004**, *126*, 14314.
[33] (a) Fritsch, P. *Liebigs. Ann. Chem.* **1984**, *272*, 319. (b) Buttenberg, W. P. *Liebigs. Ann. Chem.* **1984**, *272*, 324. (c) Wiechell, H. *Liebigs. Ann. Chem.* **1984**, 337. (d) Shi Shun, A. L. K.; Chernick, E. T.; Eisler, S.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 1339.

alkyne **7** with 1-octyne (**8**), as reported by Zweifel,[34] provided diyne **10** in 64% yield. Subsequent desilylative bromination with NBS and catalytic $AgNO_3$[35] generated **4** in 72% yield as shown in Scheme 3.

Scheme 3

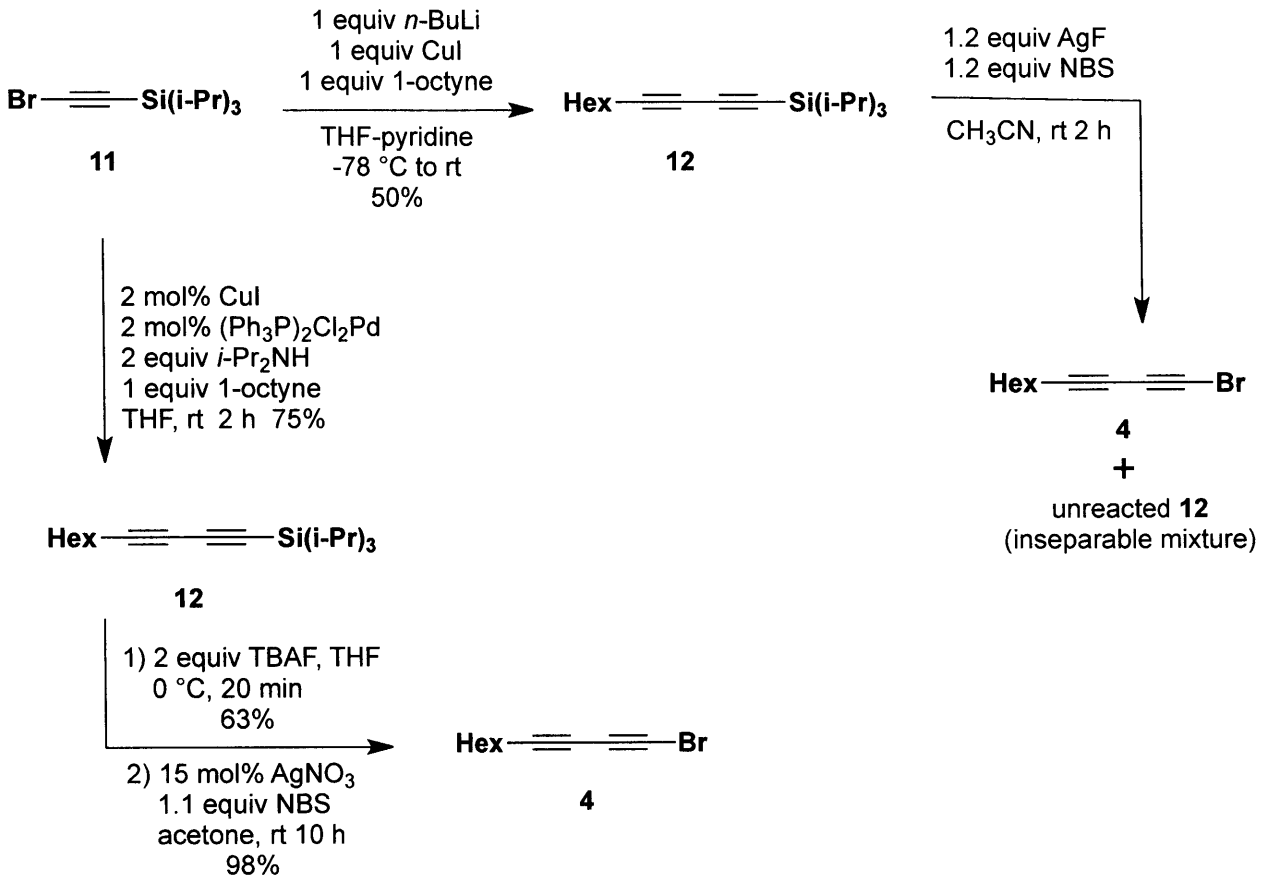


Alternatively, coupling of 1-octyne with bromo alkyne **11** produced diyne **12** in 50% yield (Scheme 4). Treatment of this diyne with AgF and NBS[36] in acetonitrile afforded an inseparable mixture of **4** with **12**. The reaction was improved by modifying the Cadiot-Chodkiewicz conditions to furnish diyne **12** in 75% yield. In addition, by performing the

[34] Miller, J. A.; Zweifel, G. *Synthesis* **1983**, 128.
[35] Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, *7*, 485.
[36] Kim, S.; Kim, S.; Lee, T.; Ko, H.; Kim, D. *Org. Lett.* **2004**, *6*, 3601.

desilylation and bromination in separate steps, **4** could then be cleanly isolated.

Scheme 4



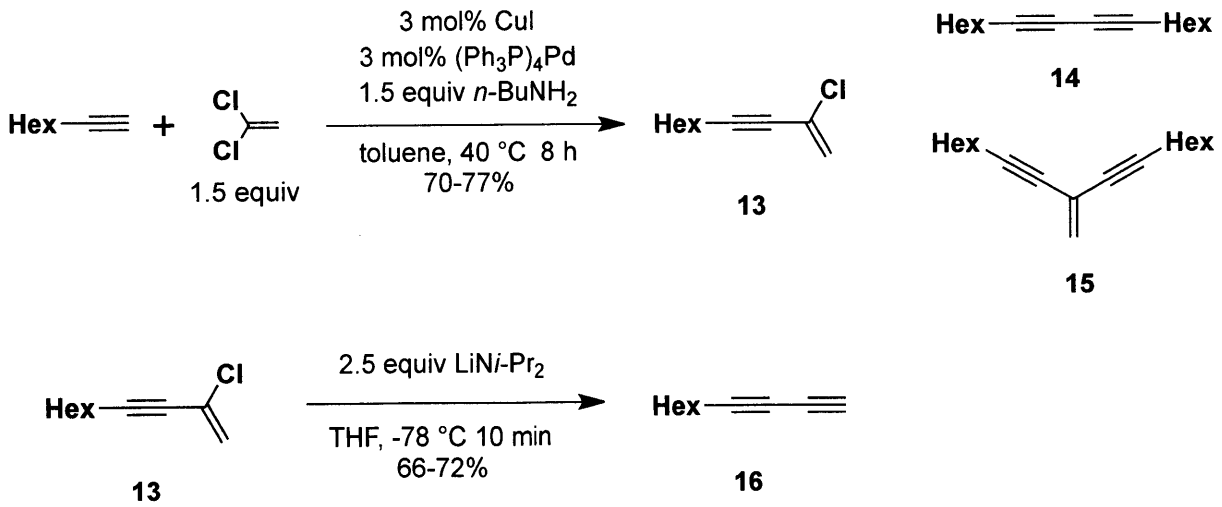
We ultimately found the most successful and economical route to conjugated diyne **4** when we turned to a new two-carbon homologation strategy developed by Negishi.[37] Negishi reported that Sonogashira coupling of 1-octyne with excess 1,1-dichloroethylene furnished 2-chloro-1-decen-3-yne (**13**) without homocoupling of 1-octyne; however, our attempts to reproduce Negishi's results led to undesired reaction pathways such as dimerization of octyne

[37] Qian, M.; Negishi, E. *Org. Proc. Res. & Dev.* **2003**, *7*, 412.

and double coupling to vinylidene chloride giving rise to the enediyne **15** (Scheme 5).

By modifying Negishi's conditions, we found that the formation of side products could be drastically suppressed for both the cross coupling and the elimination step.[38] The optimized cross coupling procedure has several benefits including a reduction in the amounts of vinylidene chloride (5.0 equiv to 1.5 equiv), $(PPh_3)_4Pd$ (5 mol% to 3 mol%), and CuI (5 mol% to 3 mol%), and a more facile isolation procedure for enyne **13**. The reaction is most successful when conducted in a sealed pressure flask in warm toluene. Without the use of a sealed flask or tube, the loss of vinylidene chloride increased the propensity for alkynyl homocoupling and for enediyne formation. The isolation procedure involves column chromatography of the concentrated reaction mixture, thereby avoiding the more time-consuming practices of an aqueous work-up and distillation. In this fashion, the desired enynyl chloride (**13**) was obtained reproducibly in 70-77% yield on scales producing 12-13 g of product.

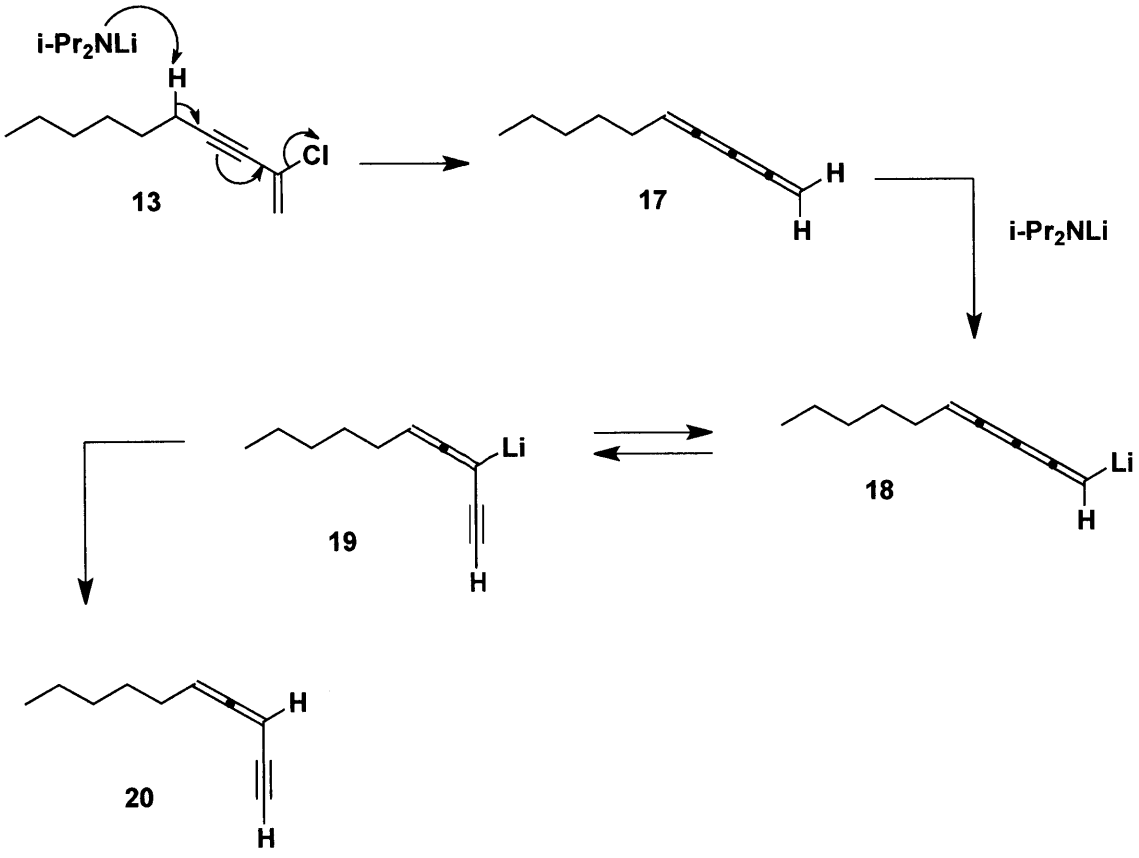
Scheme 5



[38] Kohnen, A. L.; Dunetz, J. R.; Danheiser, R. L. *Org. Synth.* **2007**, *84*, 77.

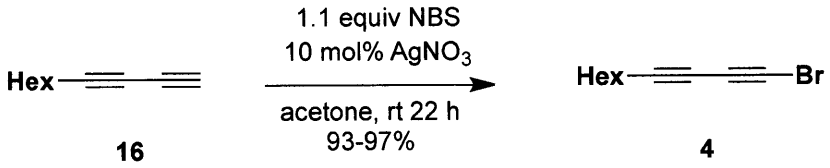
The base-mediated elimination of enyne **13** to terminal diyne **16** was initially complicated by an unexpected side product identified by ^{1}H NMR to be undeca-3,4-diene-1-yne (**20**). We surmise that the mechanism of this allenyne formation involves abstraction of the propargyl hydrogen by LDA to eliminate lithium chloride (Scheme 6). The possibility of isomerizing 1,3-decadiyne to the allenyne **20** has been ruled out based on several isomerization experiments. In one experiment, terminal diyne **16** was subjected to 1.5 equiv of LDA in THF at -78 °C for 1.5 h. Analysis of the crude ^{1}H NMR revealed only the presence of diyne **16**.

Scheme 6



In another isomerization experiment, a 2:1 mixture of **16** and **20** was exposed to 1.5 equiv of LDA in THF at -78 °C for 1.5 h, which resulted in the conversion of the allenyne to an unidentifiable polymer (separated by column chromatography) while diyne **16** was recovered in a yield of 67% based on the weight of the starting mixture. According to additional optimization studies on this transformation, we have determined that the competing elimination pathway may be circumvented by the slow addition of chloro enyne **13** as a dilute solution (ca. 1M) in THF to the LDA solution in order to minimize local heating resulting from the exothermic formation of **16**. Thus, the allenyne pathway is suppressed by maintaining the internal temperature of the reaction mixture below -65 °C.

With diyne **16** in hand, subsequent bromination with NBS and catalytic $AgNO_3$ provided **4** in excellent yield (93-97%) without purification (eq 3). Direct use of **4** in the optimized N-alkynylation coupling with carbamate **3** gave rise to diynamide **5** (>7 g product) in 82% yield (eq 2) as shown earlier.[39]



(3)

[39] Kohnen, A. L.; Dunetz, J. R.; Danheiser, R. L. *Org. Synth.* **2007**, *84*, 88.

Chapter 2

Synthesis of 3-Aminocyclobutenones via [2 + 2] Cycloaddition of Ynamides and Ketenes

Synthesis of Cyclobutenones

Cyclobutenones are valuable synthetic intermediates that have been exploited in a variety of transformations.[40] The most direct route by which to access cyclobutenone derivatives employs [2 + 2] cycloaddition reactions of ketenes with alkynes.[41] Unfortunately, unactivated (alkyl-substituted) alkynes only react with highly electrophilic ketenes such as dichloroketene.[42] Electron-rich alkynes, in particular alkoxy alkynes[43] and siloxyacetylenes,[44] combine with a wide range of ketenes.

Amino alkynes[45] are also reactive towards ketenes; however, these reactions often lead to mixtures of the desired cyclobutenones accompanied by allenyl amides such as **23**. This side

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[40] For reviews, see: (a) Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *100*, 820. (b) *Science of Synthesis: Houben Weyl Methods of Molecular Transformations*; de Meijere, A., Ed.; Thieme: Stuttgart, 1997; Vol. E17f. (c) Moore, H. W.; Yerxa, B. R. *Advances in Strain in Organic Chemistry*; Halton, B. Ed.; Jai Press: London, 1995; Vol. 4, pp 81-162. (d) Namyslo, J. C; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.

[41] For reviews, see: (a) Hyatt, J. A.; Raynolds, P. W. Ketene Cycloadditions. *Org. React.* **1994**, *45*, 159-646. (b) Tidwell, T. T. *Ketenes, 2nd Ed.;* Wiley & Sons: New York, 2006. (c) *Science of Synthesis: Houben Weyl Methods of Organic Chemistry*; Danheiser, R. L., Ed; Thieme: Stuttgart, 2006; Vol 23.

[42] (a) Hassner, A.; Dillon, J. L., Jr. *J. Org. Chem.* **1983**, *48*, 3382. (b) Danheiser, R. L.; Sard, H. *Tetrahedron Lett.* **1983**, *24*, 23. (c) Danheiser, R. L.; Savariar, S.; Cha, D. D.; *Org. Synth.* **1990**, *68*, 32.

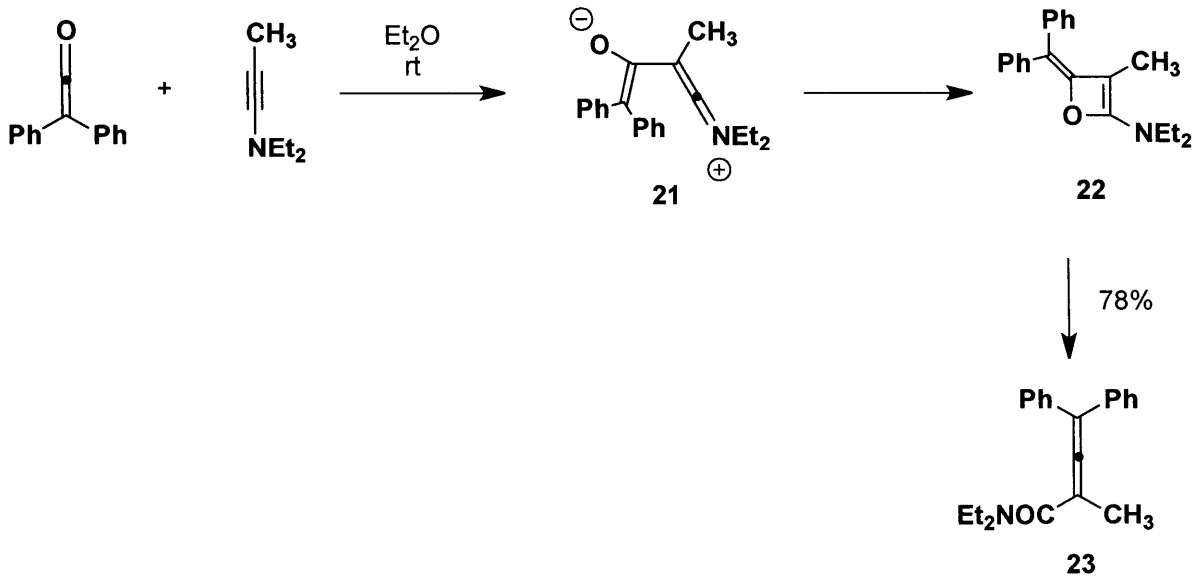
[43] For representative examples, see: (a) Rosebeck, B.; Arens, J. F. *Rec. Trav. Chim. Pays-Bas* **1962**, *81*, 549. (b) Hasek, R. H.; Gott, G. P.; Martin, J. C. *J. Org. Chem.* **1964**, *29*, 1239. (c) Ficini, J.; Genêt, J. P. *Tetrahedron Lett.* **1975**, *15*, 2633. (d) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672.

[44] (a) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917. (b) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693.

[45] For some examples, see: (a) Ficini, J. *Tetrahedron* **1976**, *32*, 1449. (b) *Science of Synthesis: Houben Weyl Methods of Molecular Transformations*; Himbert, G., Kropf, E., Schaumann, E., Eds.; Thieme: Stuttgart, 1993; Vol. E15e, pp 3267–3443. (c) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575.

reaction arises from addition of the ynamine to the ketene carbonyl group to form the alkylideneoxete (**22**) shown in Scheme 7. Electrocyclic ring opening then transforms this strained intermediate into the allenyl carboxamide (**23**).[46]

Scheme 7



In order to suppress the "abnormal" reaction leading to oxetes and allenes, we have focused our attention on reactions of ynamides, in which the nucleophilicity is attenuated by the electron-withdrawing substituent on the nitrogen atom. In this thesis we report the results of our initial synthetic survey of [2 + 2] cycloadditions of ketenes with various types of ynamides.[47]

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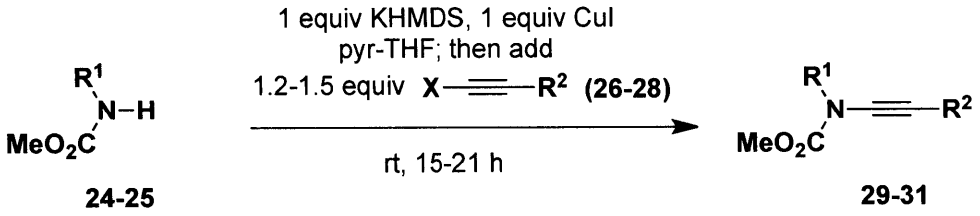
[46] (a) Kuehne, M. E.; Sheeran, P. J. *J. Org. Chem.* **1968**, *33*, 4406. (b) Truce, W. E.; Bavry, R. H.; Bailey, P. S., Jr. *Tetrahedron Lett.* **1968**, 5651. (c) Delaunois, M.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 72. (d) Ficini, J.; Pouliquen, J. *Tetrahedron Lett.* **1972**, *12*, 1135. (e) Himbert, G. *Liebigs Ann. Chem.* **1979**, 829. (f) Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1987**, *52*, 3289. (g) Schulte, N.; Möller, M. H.; Rodewald, U.; Würthwein, E.-U. *Chem. Ber.* **1994**, *127*, 1287.

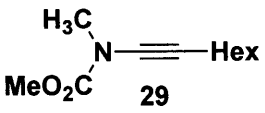
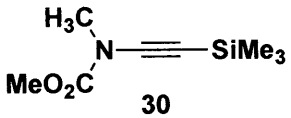
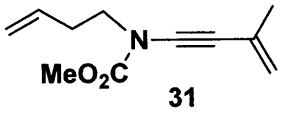
[47] Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* **2006**, *62*, 3815.

[2 + 2] Cycloaddition of Ynamides with Ketenes

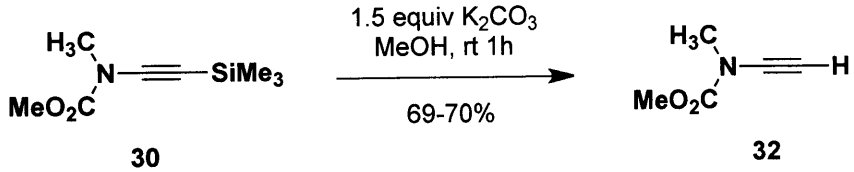
Ynamides **29** - **31** were prepared as shown in Table 2. Dr. X. Y. Mak synthesized ynamide **32**, which was obtained upon desilylation of **30** as illustrated in eq 4.

Table 2. Synthesis of ynamides by alkynylation of carbamates



entry	carbamate	halo alkyne	ynamide	yield (%)[a]
1	**24** $R^1 = CH_3$	**26** X = Br, R^2 = Hex	 **29**	61
2	**24** $R^1 = CH_3$	**27** X = I, $R^2 = SiMe_3$	 **30**	64
3	**25** $R^1 = (CH_2)_2CH{=}CH_2$	**28** X = Br, $R^2 = C(CH_3){=}CH_2$	 **31**	68

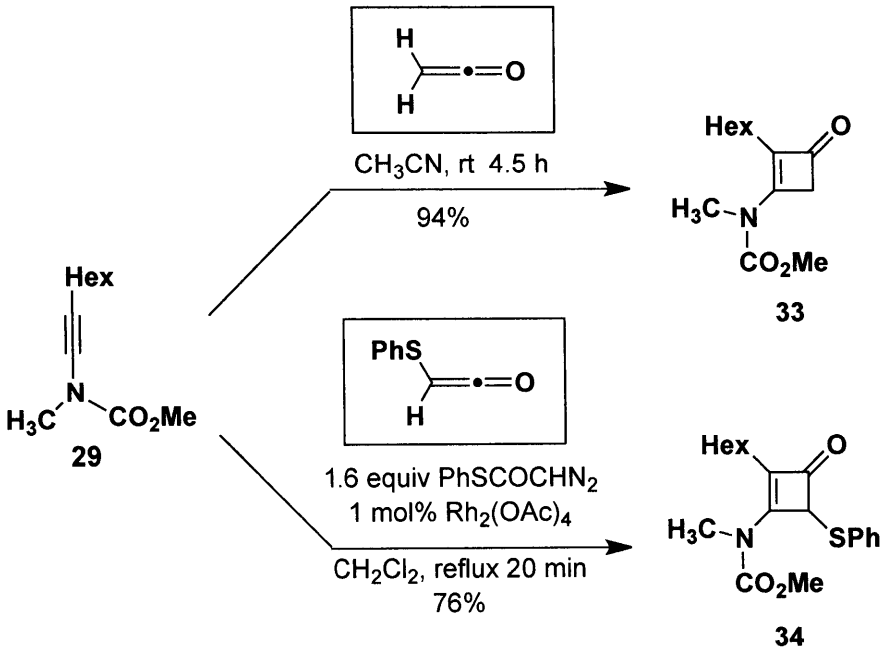
[a] Isolated yields of products purified by column chromatography.



(4)

Ynamide **29** was employed as an initial test substrate to investigate the reaction of ynamides with several classes of ketenes as depicted in Schemes 9 and 10. This ynamide combines readily with various ketenes in high yield. No evidence for the formation of oxete or allene byproducts was detected in these reactions.

Scheme 9



Cycloaddition of octynyl amide **29** with ketene afforded the desired cyclobutenone **33** in high yield after purification by column chromatography. The formation of cyclobutenone **33** was recognized by the characteristic carbonyl stretch ($\nu_{C=O}$) in the IR spectrum of the enone at 1738 cm^{-1} in addition to the alkene absorption ($\nu_{C=C}$) at 1611 cm^{-1}. For this reaction, ketene was

generated by pyrolysis of acetone in a "ketene lamp," according to the procedure of Williams and Hurd,[48] and bubbled into a 0.5 M solution of the ynamide in acetonitrile.

Although reaction of ketene with alkoxy acetylenes is well known,[45] to our knowledge only a few examples of reactions with ynamines[48c,49] and none with ynamides have been reported previously. In general, ketene reacts only with activated π bonds due to competitive facile dimerization.

Reaction of **29** with (phenylthio)ketene also proceeded smoothly to furnish **34** in 76% yield when this ketene was generated in situ by our $Rh_2(OAc)_4$-catalyzed "thia-Wolff rearrangement" of S-phenyl-2-diazoethanethioate.[50]

Dichloroketene is considerably more reactive in [2 + 2] cycloadditions than ketene, and its reaction with a variety of alkynes has previously been reported.[42] As shown in Scheme 10, generation of dichloroketene via reductive chlorination of trichloroacetyl chloride with zinc-copper couple[42c] in the presence of ynamide **29** afforded the desired amino cyclobutenone **35** in 88% yield.[51] While investigating this transformation, Dr. X. Y. Mak found that the method used for generating dichloroketene is particularly important in obtaining good yields of the desired cyclobutenone. For example, dehydrohalogenation of trichloroacetyl chloride upon treatment with Et_3N and subsequent reaction with ynamide **29** provided cyclobutenone **35** in only 35% yield. However, the use of a zinc-copper couple prepared from Zn and $CuSO_4 \cdot 5H_2O$ to effect dehalogenation of trichloroacetyl chloride resulted in successful [2 + 2] cycloaddition. To our

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[48] (a) Williams, J. W.; Hurd, C. D. *J. Org. Chem.* **1940**, *5*, 122. (b) Hanford, W. E.; Sauer, J. C. *Org. React.* **1946**, *3*, 108-140.

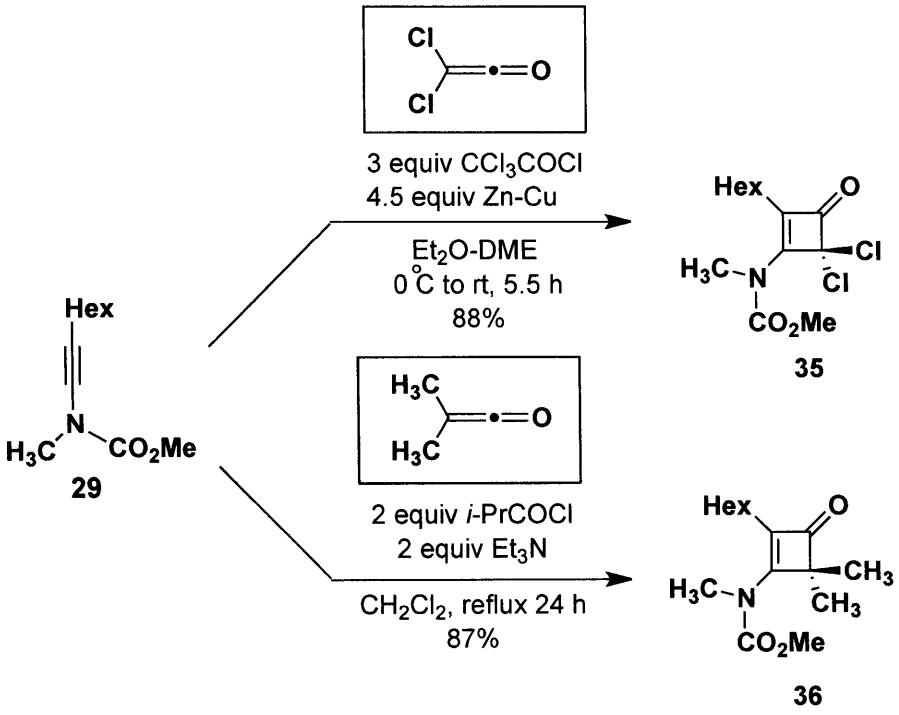
[49] (a) Henn, L.; Himbert, G. *Chem. Ber.* **1981**, *114*, 1015. (b) Henn, L.; Himbert, G.; Diehl, K.; Kaftory, M. *Chem. Ber.* **1986**, *119*, 1953.

[50] Lawlor, M. D.; Lee, T. W.; Danheiser, R. L. *J. Org. Chem.* **2000**, *65*, 4375

[51] This transformation was carried out by Dr. X. Y. Mak.

knowledge, no examples of addition of dichloroketene to ynamines or ynamides have been previously reported.

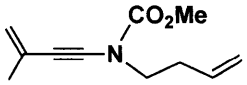
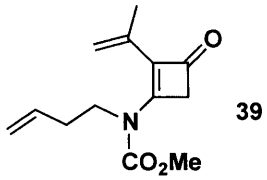
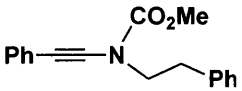
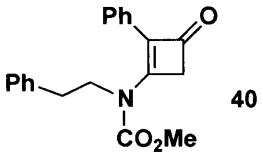
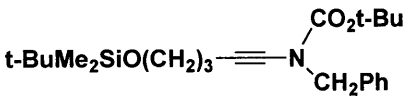
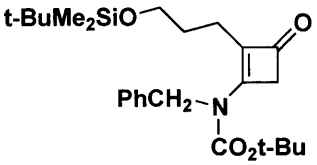
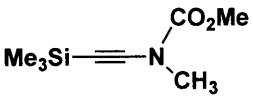
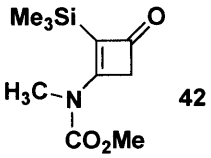
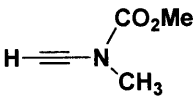
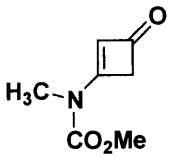
Scheme 10



Finally, addition of dimethylketene to ynamide **29** also proceeded in excellent yield (87%) when the ketene was formed in situ via dehydrohalogenation of isobutyryl chloride with triethylamine. It is worth noting that this reaction is most successful when carried out at reflux in CH_2Cl_2 as opposed to Et_2O. Reaction in Et_2O resulted in the formation of only 11% of cyclobutenone **36**. Previously, cycloaddition of dimethylketene (generated by pyrolysis of tetramethylcyclobutanedione) with ynamines has been reported to occur in only low to moderate yields.[46a]

In addition to surveying different classes of ketenes for the [2 + 2] cycloaddition, the scope with respect to the ynamide partner was also explored. Reaction of various substituted and functionalized ynamides with ketene provides access to an array of cyclobutenone derivatives in good yield while the formation of undesired allene products is obviated (Table 3).

Table 3. [2+2] Cycloadditions of Ynamides with Ketene[a]

entry	ynamide	cycloadduct	yield (%)[b]
1[c]	 **31**	 **39**	65
2[c]	 **37**	 **40**	67 (83)[d]
3	 **38**	 **41**	86
4	 **30**	 **42**	17
5	 **32**	 **43**	80

[a]Reactions were conducted using excess ketene in CH_3CN (0.2 M) at rt for 8 h. [b]Isolated yields of products purified by column chromatography. [c]The reaction was conducted in the absence of solvent for 42-44 h. [d]Yield based on recovered ynamide.

Our studies have shown that in addition to the use of acetonitrile as the solvent, CH_2Cl_2, THF, and toluene may alternatively be used with similar results. The [2 + 2] cycloaddition of ynamides **31**[52] and **37** with ketene proved sluggish due to the inductive effect of the unsaturated substituents attached to the alkyne; however, these cycloadditions did proceed at a reasonable rate and in good yield when conducted in the absence of solvent. It is noteworthy that addition of ketene to enynamide **31** occurs exclusively at the triple bond; no products were detected resulting from addition of ketene to either the conjugated double bond or the terminal olefin of the butenyl substituent of **31**. Cycloaddition of Boc-protected ynamide **38** with ketene provided **41** in excellent yield. Not surprisingly, reaction of silyl ynamide **30** with ketene produced cyclobutenone **42** in poor yield. The relatively low reactivity of **30** may be attributed to non-bonded steric interactions between the approaching ketene and the trimethylsilyl group; however, Dr. X. Y. Mak demonstrated that deprotection of ynamide **30**, to unmask the terminal alkyne, and reaction of this product (**32**) with ketene provides cyclobutenone **43** in 80% yield.

[52] Dr. X. Y. Mak prepared this ynamide using our Cu-mediated N-alkynylation coupling method.

Part II

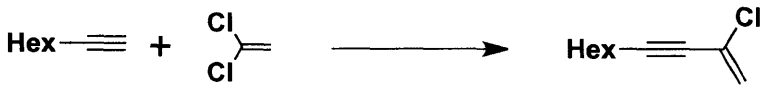
Experimental Section

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. Thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230-400 mesh).

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. Acetonitrile, piperidine, pyridine, triethylamine, *n*-butylamine, diisopropylamine, and hexamethyldisilazane were distilled under argon from calcium hydride. Chlorotrimethylsilane, chlorotriisopropylsilane, (trifluoromethanesulfonyl)-triisopropylsilane, and trifluoromethanesulfonyl anhydride were distilled under argon from phosphorous pentoxide. Methyl chloroformate, trichloroacetyl chloride and isobutyryl chloride were distilled at atmospheric pressure under argon. Copper(I) iodide was extracted with THF for 24 h in a Soxhlet extractor and then dried under vacuum (0.1 mmHg). *N*-Bromosuccinimide was recrystallized from boiling water. 2-Bromopropene was passed through a pad of basic alumina in a disposable pipette prior to use. Vinylidene chloride was purified immediately before use by filtration through basic alumina in a glass column

(equipped with a needle at the bottom) under nitrogen pressure into a flame-dried flask equipped with a septum and an outlet needle.

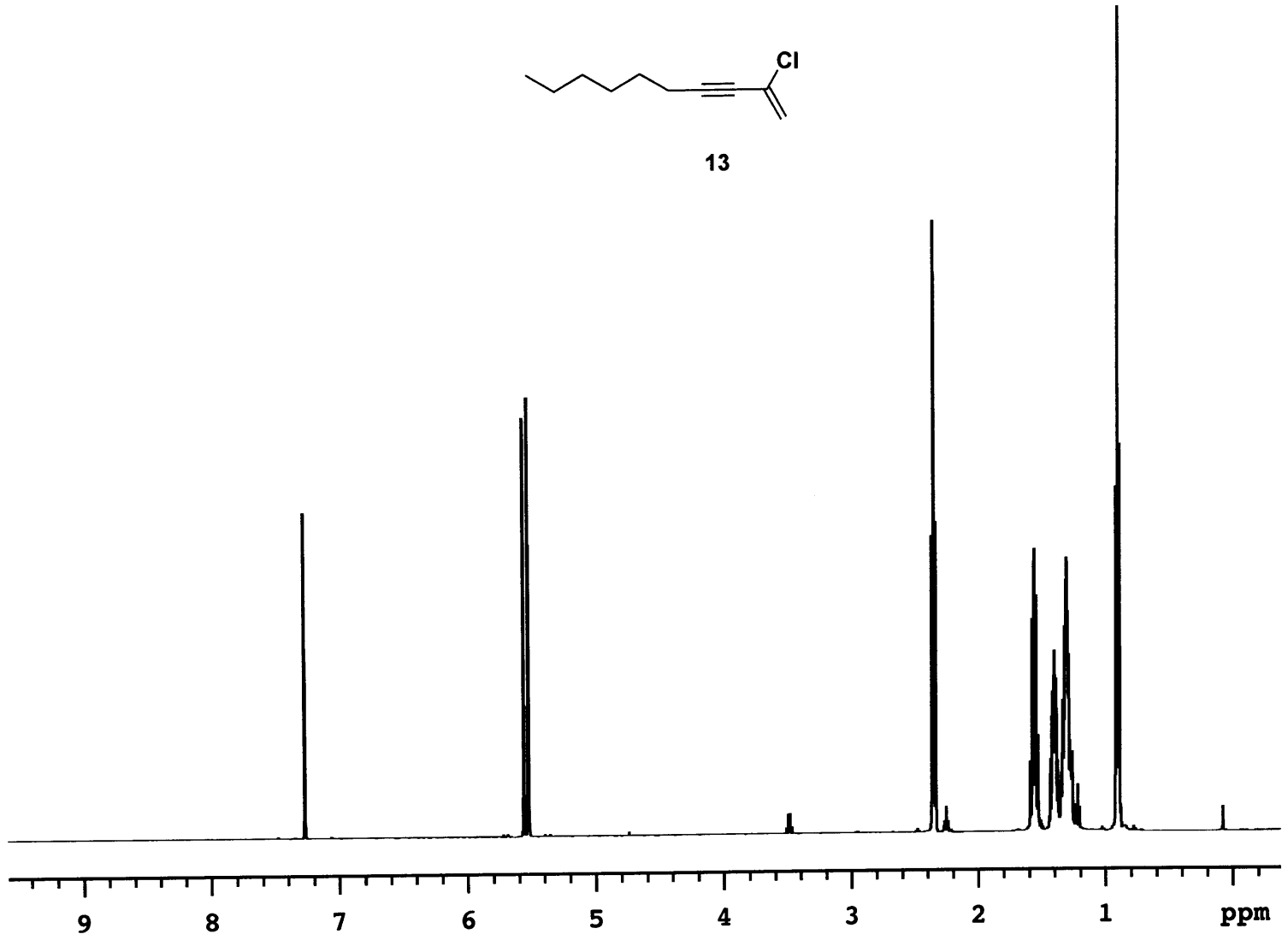
Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured with an Inova 500 spectrometer. ^{1}H NMR chemical shifts are expressed in parts per million (d) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (d) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). Low-resolution mass spectra (GC-MS) were measured on an 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. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc. of Parsippany, NJ.



13

2-Chloro-1-decen-3-yne (13).

A 350-mL threaded round-bottomed pressure flask (142 mm length x 82.5 mm O.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with $(Ph_3P)_4Pd$ (3.46 g, 2.99 mmol), vinylidene chloride (11.8 mL, 14.5 g, 150 mmol), and 150 mL of toluene. The resulting yellow mixture was stirred at room temperature for 20 min and then a mixture of 1-octyne (14.7 mL, 11.0 g, 99.8 mmol) and *n*-butylamine (14.9 mL, 11.0 g, 150 mmol) was added via cannula over 5 min (the flask is rinsed with two 3-mL portions of toluene). Copper(I) iodide (0.569 g, 2.99 mmol) was then added in one portion and material adhering to the sides of the pressure flask was rinsed into the reaction mixture with 5 mL of toluene. The pressure flask was sealed with a threaded Teflon cap and submerged in a preheated oil bath at 40 °C behind a safety shield. After 8 h, the cloudy red mixture was allowed to cool to room temperature and then filtered through a medium frit sintered glass funnel. The precipitated ammonium salt was washed with 100 mL of hexanes and the filtrate was concentrated to give a red oil (29.0 g). Column chromatography on 500 g of silica gel (elution with hexanes) afforded 11.9-13.0 g (70-76%) of the desired enyne as a yellow liquid: IR (neat) cm^{-1}: 2932, 2216, 1602, 1196; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.90 (t, J = 6.8 Hz, 3H), 1.28 – 1.34 (m, 4H), 1.40 (app quint, J = 7.0 Hz, 2H), 1.55 (app quint, J = 7.0 Hz, 2H), 2.35 (t, J = 7.3 Hz, 2H), 5.53 (s, 1 H), 5.56 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.5, 19.7, 23.0, 28.6, 29.0, 31.7, 78.0, 93.3, 120.8, 121.3. Anal. calcd. for $C_{10}H_{15}Cl$: C, 70.37; H, 8.86; found: C, 70.35; H, 8.76.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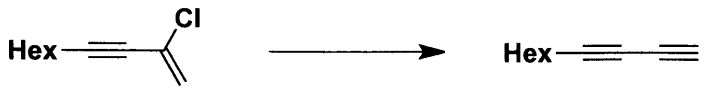
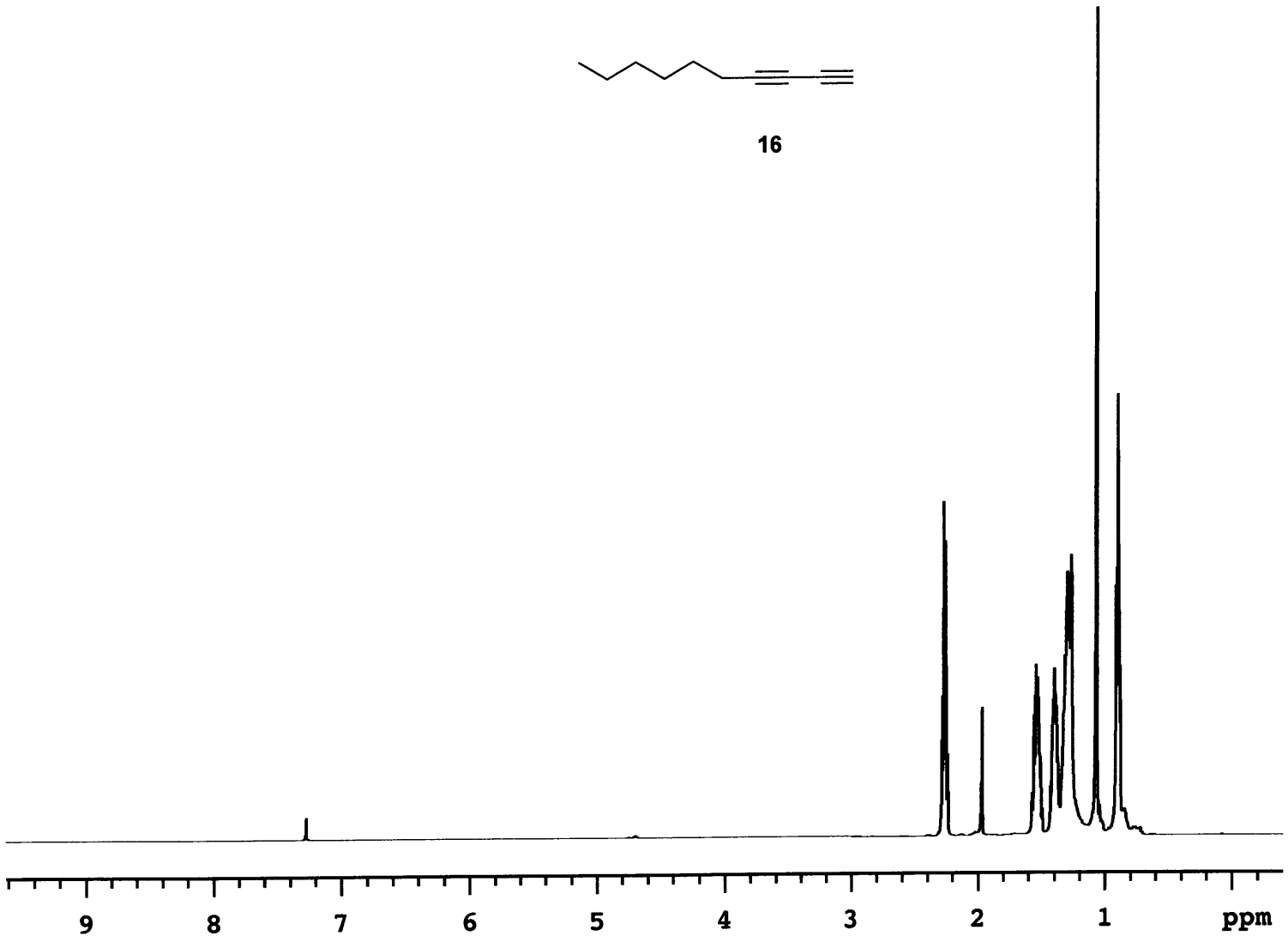


13 16

1,3-Decadiyne (16).

A 1-L, three-necked, round-bottomed flask equipped with a rubber septum, a 125-mL, pressure-equalized addition funnel fitted with a rubber septum, and a Claisen adapter fitted with a rubber septum and an argon inlet adapter was charged with a solution of diisopropylamine (23.4 mL, 16.9 g, 167 mmol) in 200 mL of THF. The solution was cooled at 0 °C and *n*-butyllithium (2.39 M in hexane, 67.4 mL, 161 mmol) was added via the addition funnel dropwise over 15 min. The resulting yellow solution was stirred at 0 °C for 30 min and then cooled to –78 °C. To this solution was added a solution of enynyl chloride **13** (11.0 g, 64.4 mmol) in 80 mL of THF (pre-cooled to –78 °C) via cannula over 20 min (the flask was washed with two 5-mL portions of THF). After 5-10 min the red mixture was poured into a 1-L separatory funnel containing 100 mL of half-saturated NH_4Cl solution, diluted with 150 mL of pentane, and extracted with 100 mL of 10% HCl solution. The organic phase was separated and washed with two 100-mL portions of 10% HCl and the combined aqueous phases are back-extracted with two 100-mL portions of pentane. The combined organic layers were washed with 100 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 9.28 g of a red liquid. Column chromatography on 300 g of silica gel (elution with pentane) provided 5.67-6.70 g (66 –72%) of diyne **16** as an orange liquid: IR (neat) cm^{-1}: 3311, 2931, 2226, 1467; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.0 Hz, 3H), 1.25-1.34 (m, 4H), 1.40 (app quint, J = 7.0 Hz, 2H), 1.54 (app quint, J = 7.3 Hz, 2H), 1.97 (s, 1 H), 2.26 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125

MHz, $CDCl_3$) δ: 14.2, 19.2, 22.7, 28.2, 28.7, 31.5, 64.6, 64.8, 68.8, 78.9. Anal. calcd. for $C_{10}H_{14}$: C, 89.49; H, 10.51; found: C, 89.36; H, 10.61.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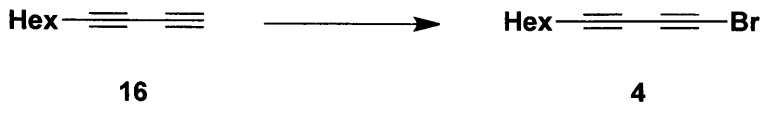
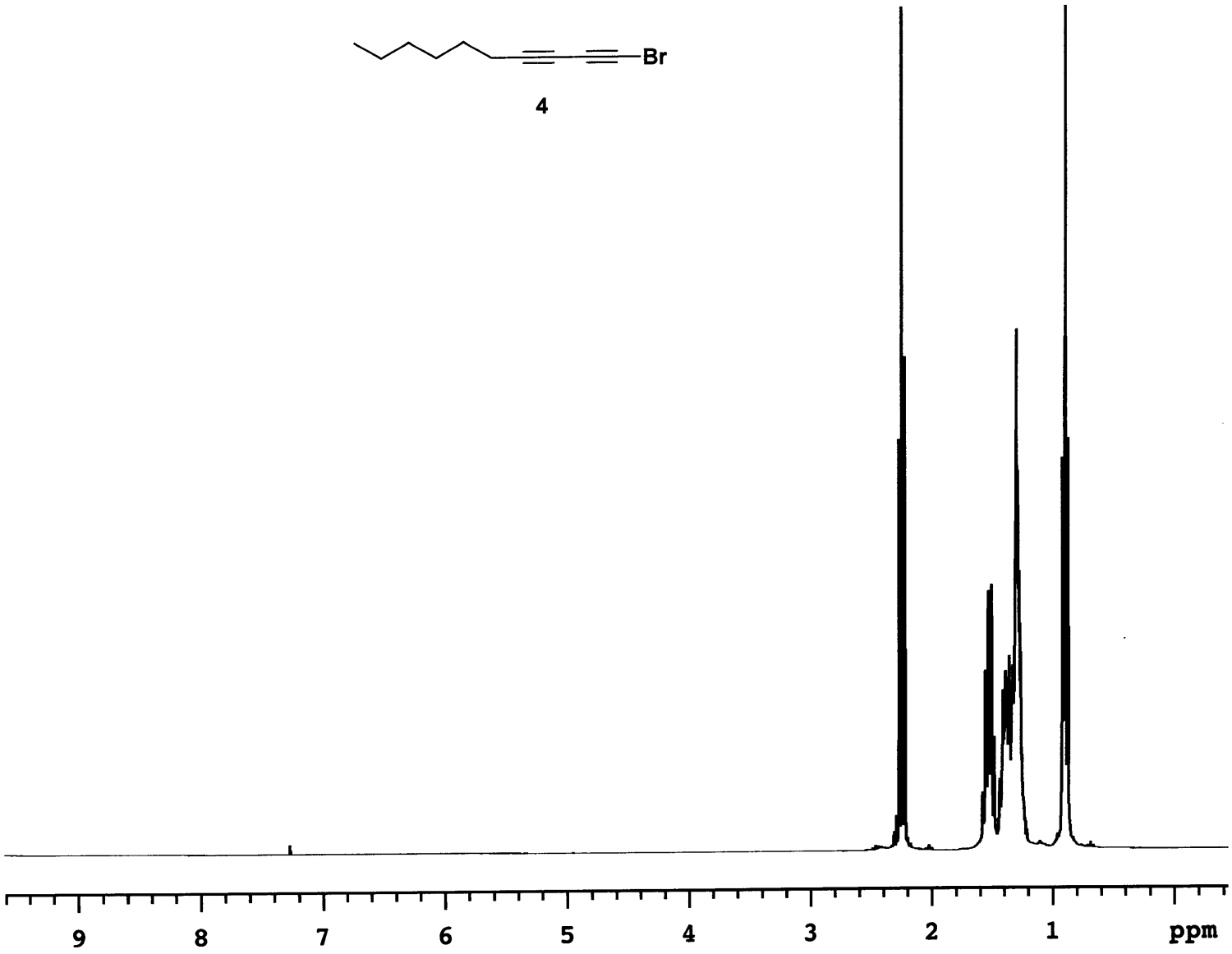


16 4

1-Bromo-1,3-decadiyne (4).

A 200-mL, one-necked, round-bottomed flask equipped with a rubber septum, and argon inlet needle was charged with 1,3-decadiyne (**14**) (5.67 g, 42.2 mmol), 100 mL of acetone, *N*-bromosuccinimide (8.26 g, 46.4 mmol) and $AgNO_3$ (0.720 g, 4.24 mmol). The rubber septum is replaced with an argon inlet adapter and the reaction mixture was stirred in the dark at room temperature for 22 h. The resulting cloudy orange mixture was diluted with 100 mL of pentane, washed with two 50-mL portions of saturated $Na_2S_2O_3$ solution, extracted with two 50-mL portions of pentane. The combined organic phases were washed with 100 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 8.44–8.71 g (93–97%) of bromo diyne **4** as a red oil: IR (neat) cm^{-1}: 2956, 2931, 2859, 2184, 2157, 1466; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.90 (t, J = 6.9 Hz, 3 H), 1.24 – 1.34 (m, 4 H), 1.38 (app quint, J = 7.0 Hz, 2 H), 1.55 (app quint, J = 7.3 Hz, 2 H), 2.25 (t, J = 7.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.5, 19.5, 23.0, 28.5, 29.0, 31.7, 37.3, 65.8, 66.2, 77.9. Anal. calcd. for $C_{10}H_{13}Br$: C, 56.36; H, 6.15; found: C, 56.36; H, 6.29.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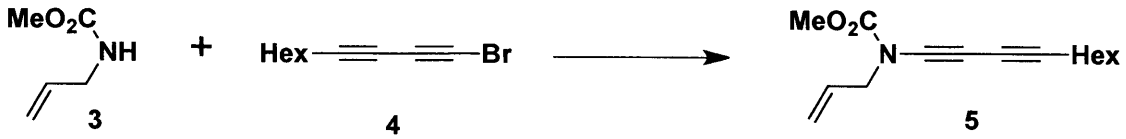
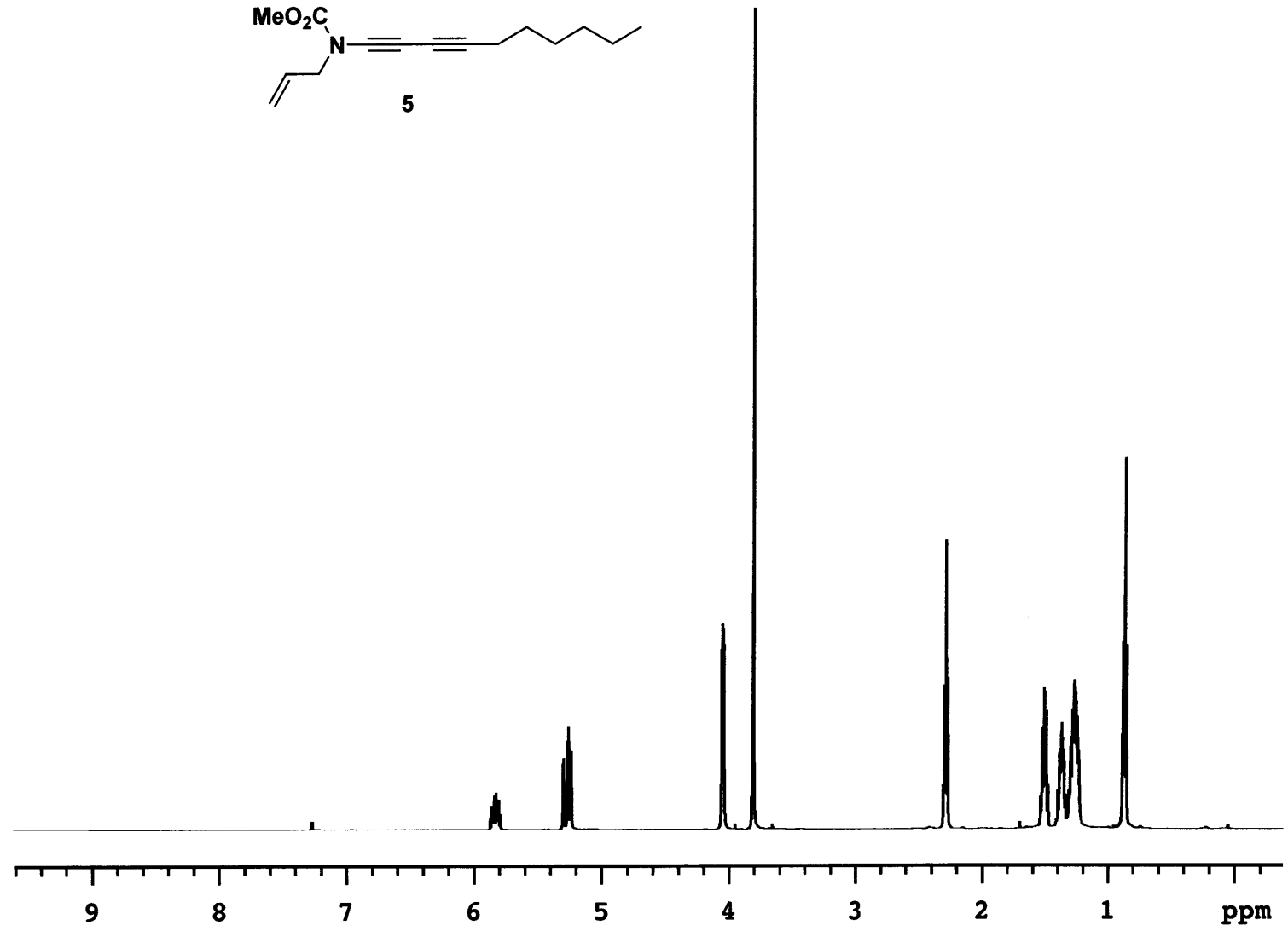


***N*-(Methoxycarbonyl)-*N*-(2-propenyl)-1,3-decadiynylamide (5).**

A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a rubber septum, and a 125-mL pressure-equalized addition funnel fitted with a rubber septum was charged with carbamate **3** (3.98 g, 34.6 mmol), 130 mL of tetrahydrofuran and 70 mL of pyridine (68.0 g, 870 mmol). The solution was cooled to 0 °C and 38 mL of potassium hexamethyldisilazide solution (0.91 M in THF, 35 mmol) was added over 10 min. The peach-colored slurry was allowed to warm to room temperature over 15 min and then copper(I) iodide (6.59 g, 34.6 mmol) was added in one portion and the resulting yellow-green mixture was stirred at room temperature for 2 h. A solution of bromo diyne **4** (8.44 g, 39.6 mmol) in 40 mL of THF was then added via the addition funnel over 45 min (5 mL THF rinse) and the resulting mixture was stirred at room temperature for 20 h. The dark red-brown reaction mixture was diluted with 150 mL of anhydrous diethyl ether, washed with four 100-mL portions of a 3:1 mixture of saturated NaCl solution and concentrated NH_4OH solution, and extracted with two 100-mL portions of Et_2O. The combined organic layers were washed with two 200-mL portions of 1M HCl solution, 200 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 18.5 g of a dark red oil. This material was purified by column chromatography on 300 g of silica gel (elution with 0- 5% EtOAc-hexanes) to provide 7.03 g (82%) of diynamide **5** as a red oil: IR (neat) cm^{-1}: 2932, 2261, 2171, 1739, 1442; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.0 Hz, 3 H), 1.24 – 1.34 (m, 4 H), 1.38 (app quint, J = 7.4 Hz, 2 H), 1.53 (app quint, J = 7.3 Hz, 2 H), 2.31 (t, J = 7.0 Hz, 2 H), 3.83 (s, 3 H), 4.07 (d, J = 6.1 Hz, 2 H), 5.27 (dd, J = 1.3, 10.5

Hz, 1 H), 5.30 (dd, J = 1.3, 18.6 Hz, 1 H), 5.85 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.3, 19.8, 22.7, 28.5, 28.8, 31.5, 52.7, 54.5, 57.9, 64.3, 67.4, 84.1, 119.3, 131.2, 155.9. Anal. calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66; found: C, 72.59; H, 8.40; N, 5.31.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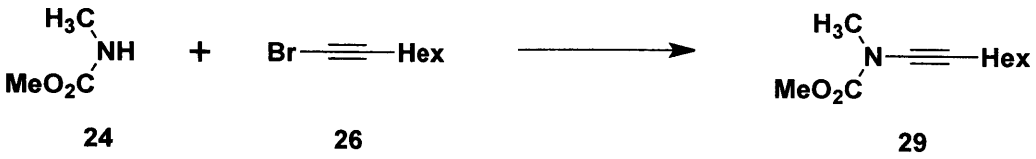
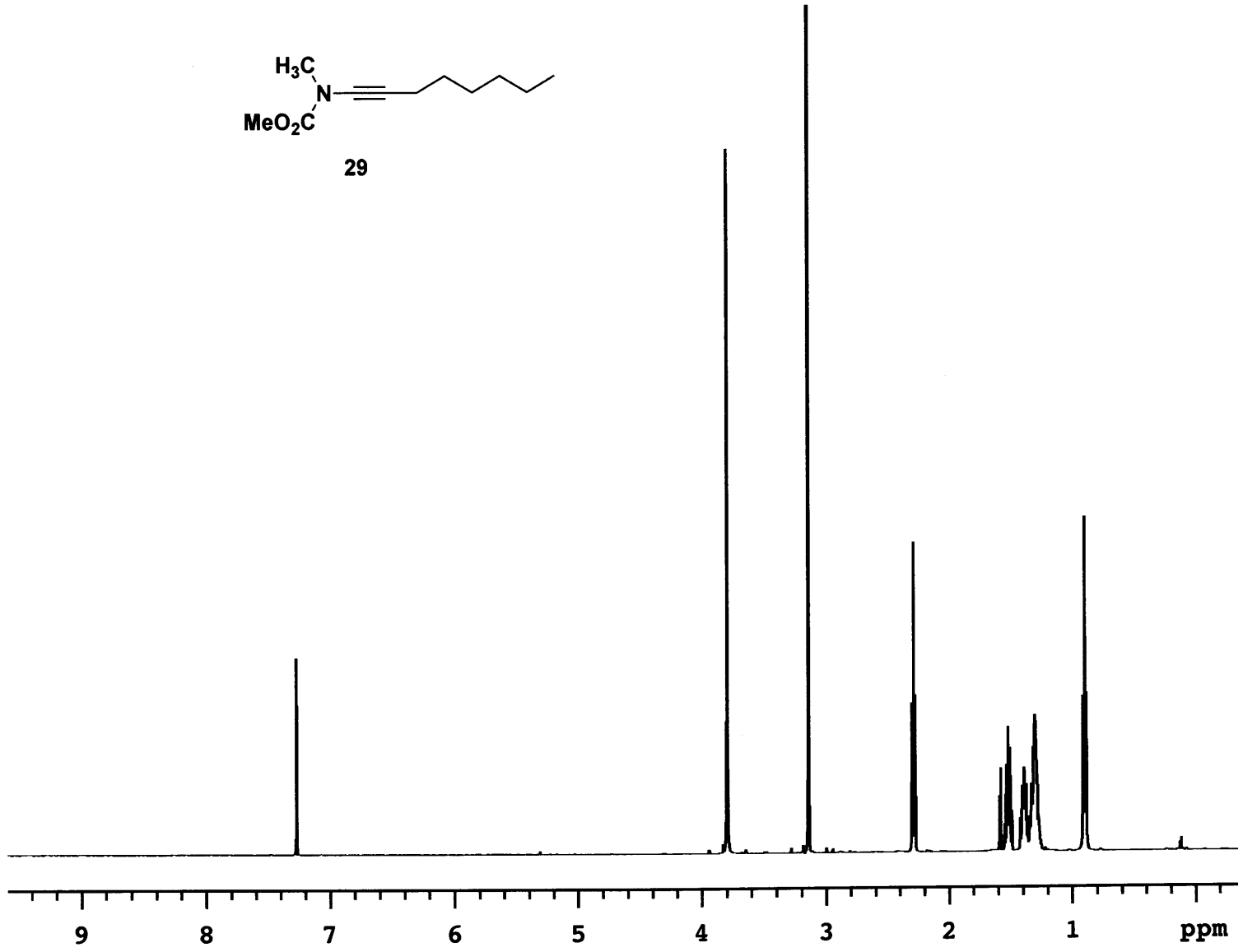


24 26 29

General Procedure for the Synthesis of Ynamides

***N*-Methyl-*N*-(octynyl)methylcarbamate (29).**

A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and an addition funnel fitted with a rubber septum was charged with carbamate **24** (1.20 g, 13.5 mmol), 60 mL of THF, and 27.3 mL of pyridine. The colorless solution was cooled at 0°C and a solution of KHMDS (0.91 M in THF, 14.8 mL, 13.5 mmol) was added dropwise over 4 min. After 15 min, CuI (2.57 g, 13.5 mmol) was added and the resulting green reaction mixture was allowed to warm to rt over 2.5 h. A solution of bromo alkyne **26** (3.06 g, 16.2 mmol) in 16 mL of THF was added via the addition funnel over 1 h and the reaction mixture was stirred for 20 h. The resulting red mixture was diluted with 50 mL of Et_2O, and washed with three 100-mL portions of a 2:1 mixture of brine and concentrated aq NH_4OH solution. The combined aqueous phases were extracted with two 100-mL portions of Et_2O, and the combined organic phases were washed with two 100-mL portions of 3 M HCl solution and 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 5.87 g of dark red oil. Column chromatography on 100 g of silica gel (gradient elution with 0-20% EtOAc-Hex) provided 1.62 g (61%) of ynamide **29** as an orange liquid: IR (neat) 3584, 2956, 2930, 2858, 2265, 1729, 1446, and 1377 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.14 (s, 3H), 2.29 (t, J = 7.2 Hz, 2H), 1.52 (m, 2H), 1.39 (m, 2H), 1.31 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 54.1, 38.2, 31.8, 31.6, 29.2, 28.7, 22.8, 18.7, 14.4, and 14.3; HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_{11}H_{19}NO_2$, 220.1308; found 220.1310.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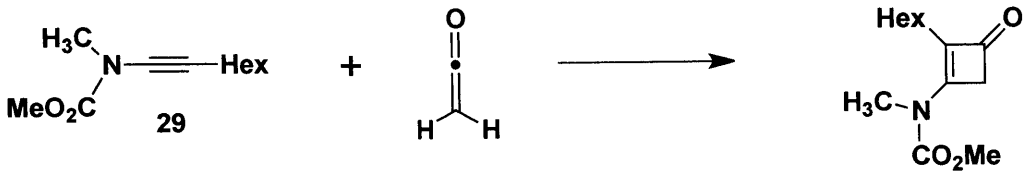
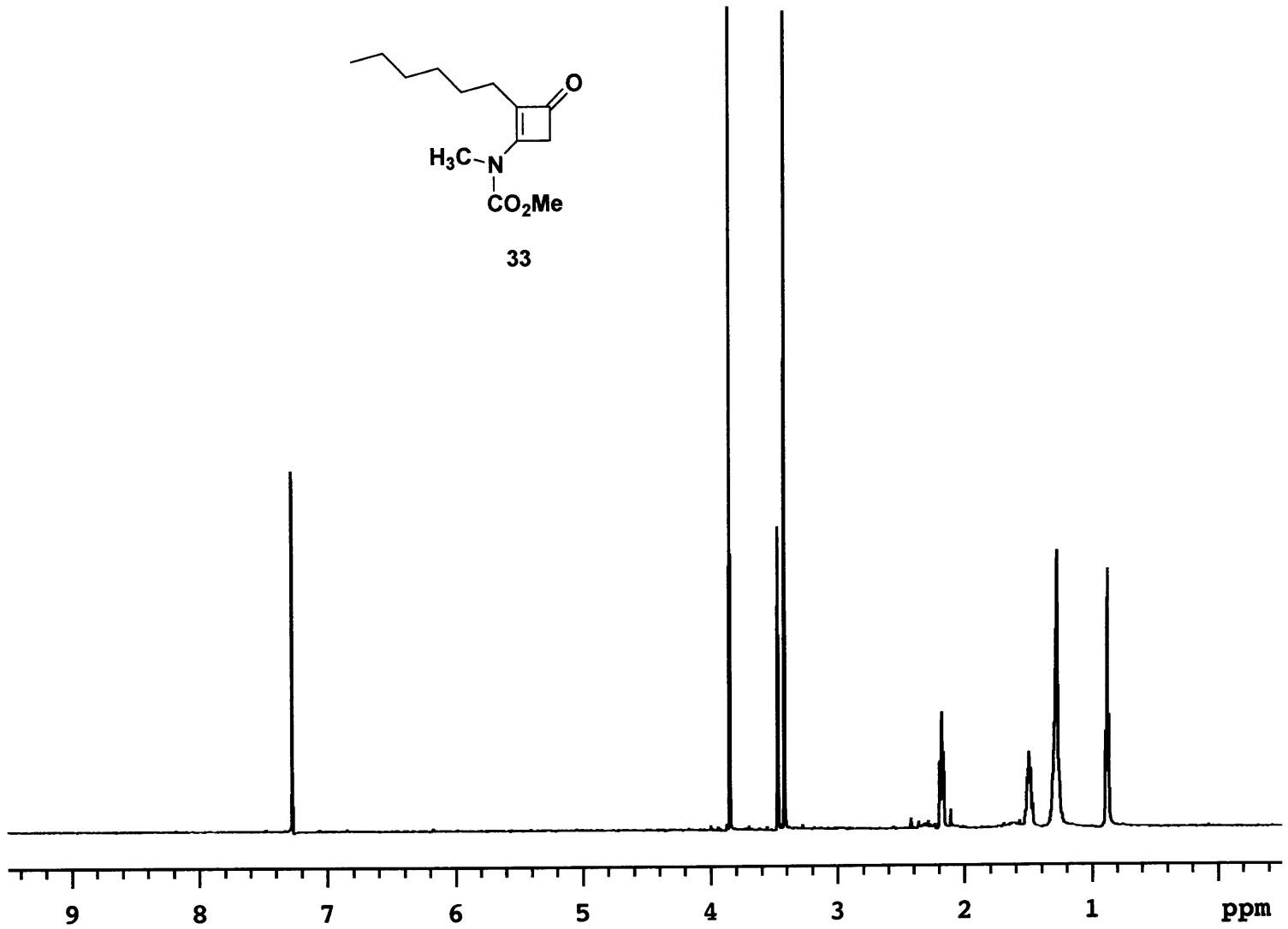


33

General procedure for the [2 + 2] cycloaddition of ketene with ynamides.

2-Hexyl-3-[*N*-(methoxycarbonyl)-*N*-methylamino]-2-cyclobuten-1-one (33).

Ketene was generated by pyrolysis of acetone over an electrically heated metal filament using the apparatus described by Williams and Hurd.[48] A two-necked, 25-mL, pear flask fitted with a rubber septum and an argon inlet adapter was charged with ynamide **29** (0.152 g, 0.77 mmol) in 1.5 mL of CH_3CN. The argon inlet adapter was replaced with an adapter fitted with a glass pipette connected via Tygon tubing to the ketene generator. The septum was fitted with an outlet needle connected via tubing to a column of $CaSO_4$ leading to a trap of H_2O. Ketene was bubbled into the reaction mixture at rt over a period of 5 h. The reaction mixture was then concentrated to afford 0.279 g of brown oil. Purification by column chromatography on 16 g of silica gel (elution with 25% EtOAc-hexanes) gave 0.184 g (94%) of **33** as a yellow oil: IR (CH_2Cl_2) 2957, 2930, 2858, 1738, 1611, 1382, 1326, and 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.44 (s, 2H), 3.39 (s, 3H), 2.15, (t, J = 7.8 Hz, 2H), 1.47 (m, 2H), 1.25 (app s, 6H), and 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 160.4, 153.9, 127.3, 54.5, 51.0, 35.4, 32.0, 29.6, 29.4, 24.1, 23.0, and 14.5; HRMS-EI m/z $[M]^+$ calcd for $C_{13}H_{21}NO_3$, 239.1516; found 239.1524.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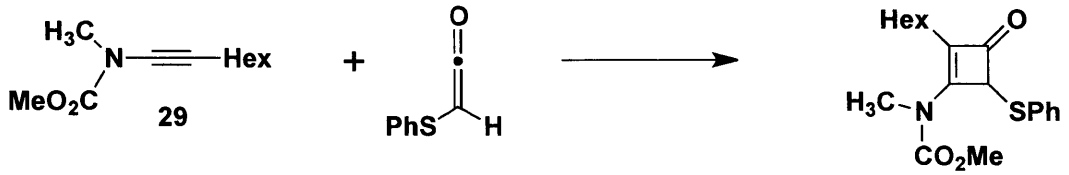
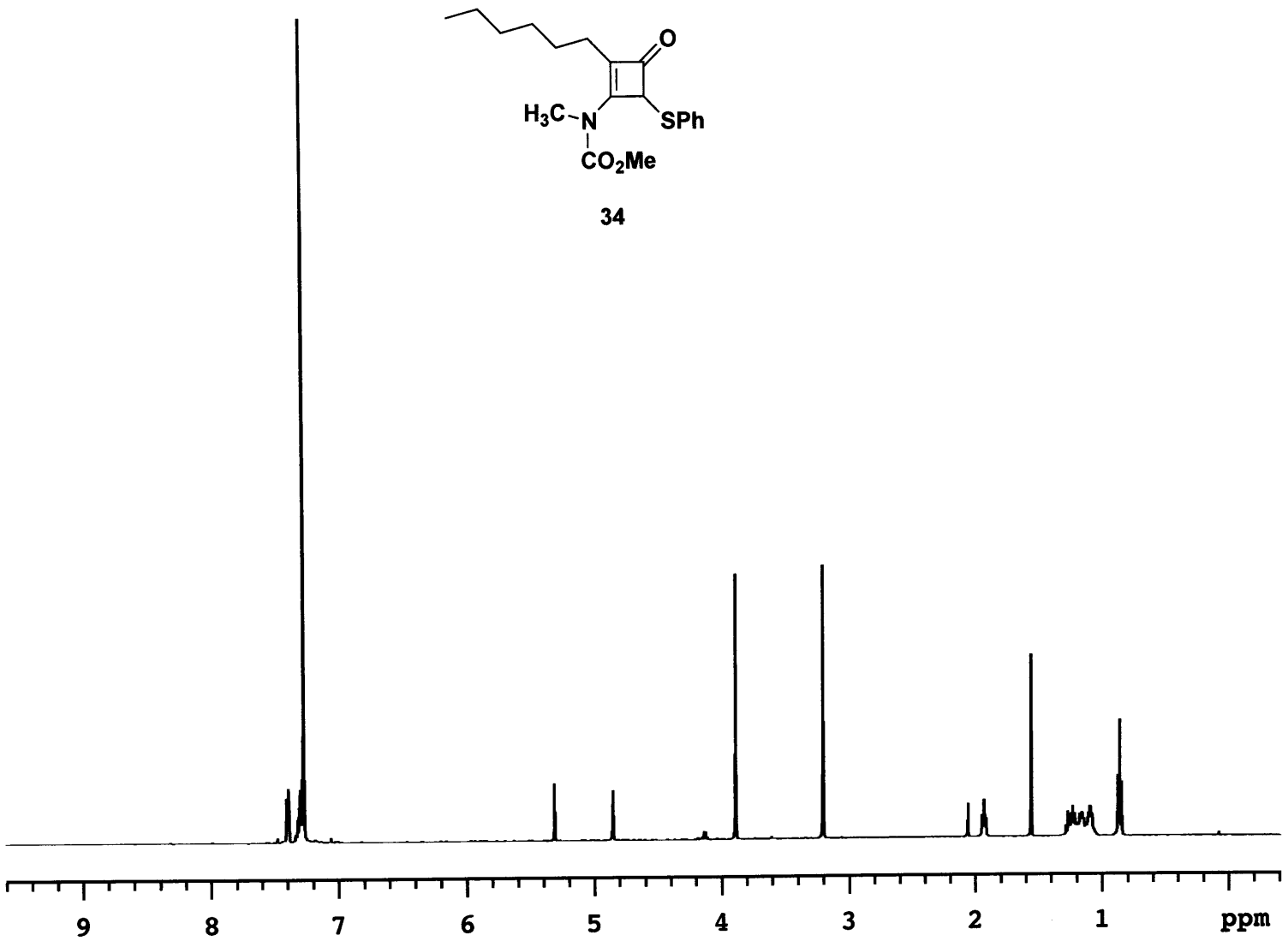


2-Hexyl-3-[*N*-(methoxycarbonyl)-*N*-methylamino]-4-phenylsulfanyl-2-cyclobuten-1-one (34).

A 25-mL, two-necked, pear flask equipped with a rubber septum and a reflux condenser fitted with an argon inlet adapter was charged with ynamide **29** (0.100 g, 0.507 mmol), 6 mL of CH_2Cl_2, and $Rh_2(OAc)_4$ (0.002 g, 0.005 mmol). The rubber septum was replaced with a 5-mL addition funnel that was then charged with a solution of $PhSCOCHN_2$ (0.145 g, 0.811 mmol) in 1.5 mL of CH_2Cl_2. The green reaction mixture was heated at reflux and the diazo thiol ester solution was added dropwise over 1 h (the funnel was rinsed with 0.5 mL of CH_2Cl_2). The resulting mixture was heated at reflux for an additional 20 min and then allowed to cool to rt. The reaction mixture was concentrated and the resulting brown oil was filtered through a column of 2 g of silica gel with the aid of 40 mL of CH_2Cl_2. The filtrate was concentrated to give 0.244 g of orange oil which was purified by column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes) to give 0.133 g (76%) of **34** as an orange oil: IR (neat) 2956, 2929, 1758, 1738, 1612, and 1379 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 7.0 Hz, 2H), 7.33 (m, 4H), 4.85 (s, 1H), 3.88 (s, 3H), 3.20 (s, 3H), 1.93 (t, 2H), 1.20 (m, 8H), and 0.86 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.0, 161.2, 153.3, 136.4, 132.3, 129.1, 129.0, 128.7, 66.0, 54.4, 35.1, 31.5, 29.2, 28.2, 23.7, 22.5, and 14.1; HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_{19}H_{25}NO_3S$, 370.1447; found 370.1440.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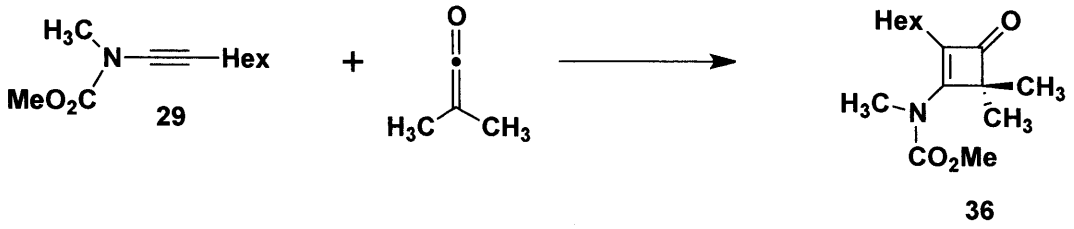
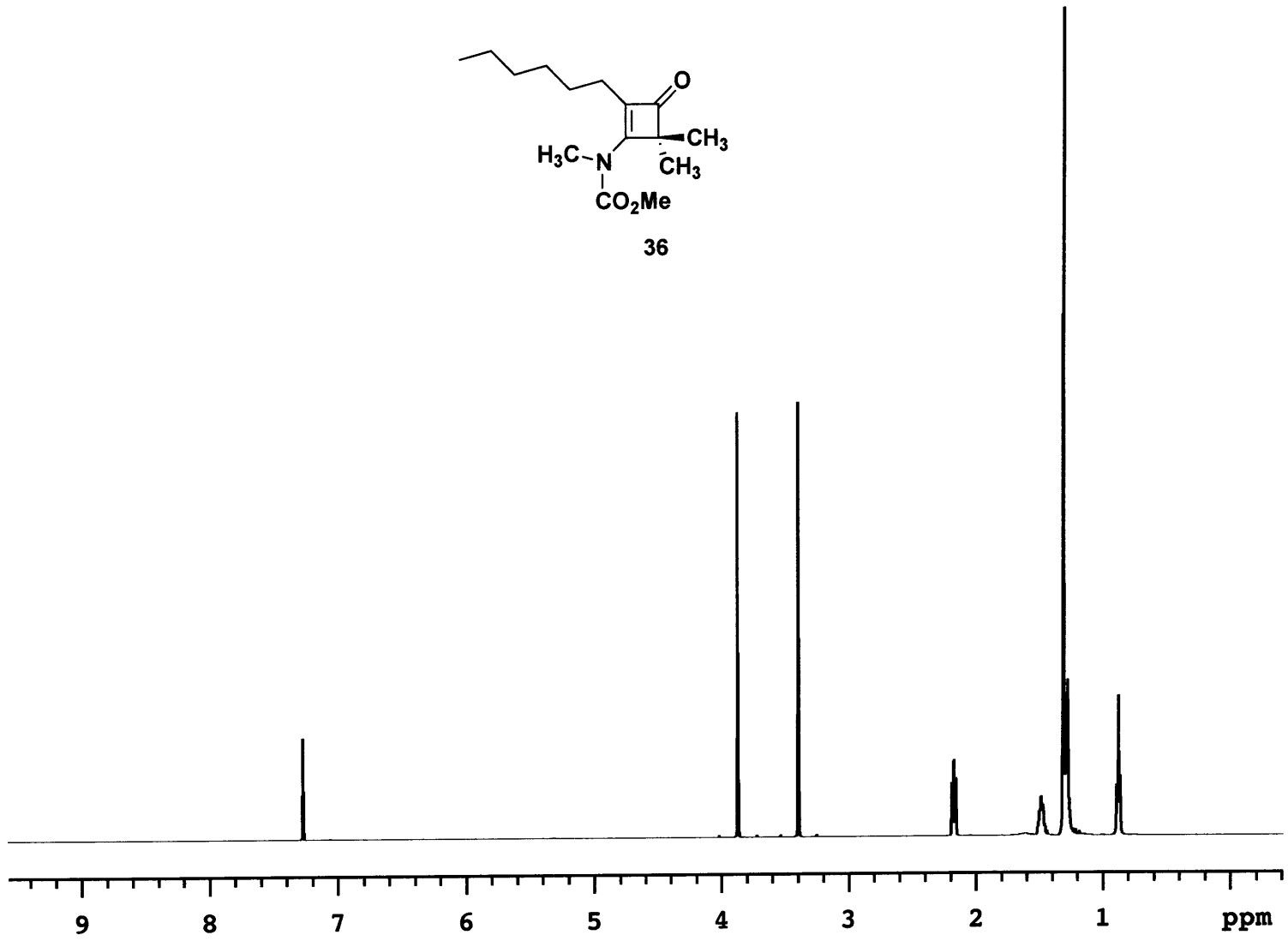


4,4-Dimethyl-2-hexyl-3-[*N*-(methoxycarbonyl)-*N*-methylamino]-2-cyclobuten-1-one (36).

A 10-mL, one-necked, pear flask equipped with a rubber septum and an argon inlet needle was charged with ynamide **29** (0.100 g, 0.507 mmol), 2 mL of CH_2Cl_2, and isobutyryl chloride (0.108 g, 0.106 mL, 1.01 mmol). A solution of Et_3N (0.113 g, 0.156 mL, 1.12 mmol) in 0.3 mL of CH_2Cl_2 was transferred into the reaction mixture via cannula over 3 min (the flask was rinsed with 0.2 mL of CH_2Cl_2). The septum was replaced with a cold finger condenser and the pink solution was heated at reflux for 24 h. The resulting heterogeneous orange mixture was allowed to cool to rt, diluted with 20 mL of CH_2Cl_2, and washed with 10 mL of 1 M HCl solution and 15 mL of H_2O. The combined aqueous phases were extracted with two 10-mL portions of CH_2Cl_2 and the combined organic phases were washed with 20 mL of 10% K_2CO_3 solution and 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.161 g of orange oil. Column chromatography on 10 g of silica gel (elution with 20% EtOAc-hexanes) provided 0.118 g (87%) of cyclobutenone **36** as a yellow liquid: IR (neat) 2957, 2928, 2361, 1751, 1602, 1449, 1379, and 1198 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.40 (s, 3H), 2.17 (t, J = 7.6 Hz, 2H), 1.48 (m, 2H), 1.31 (s, 6H), 1.28 (m, 6H), and 0.87 (t, J = 3.0 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 197.1, 169.5, 152.8, 124.6, 62.3, 53.9, 35.5, 31.7, 29.3, 29.1, 23.8, 22.7, 21.5, and 14.2; HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_{15}H_{25}NO_3$, 290.1727; found, 290.1725.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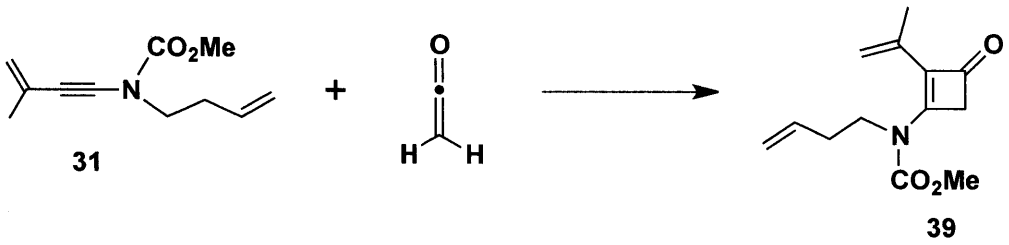
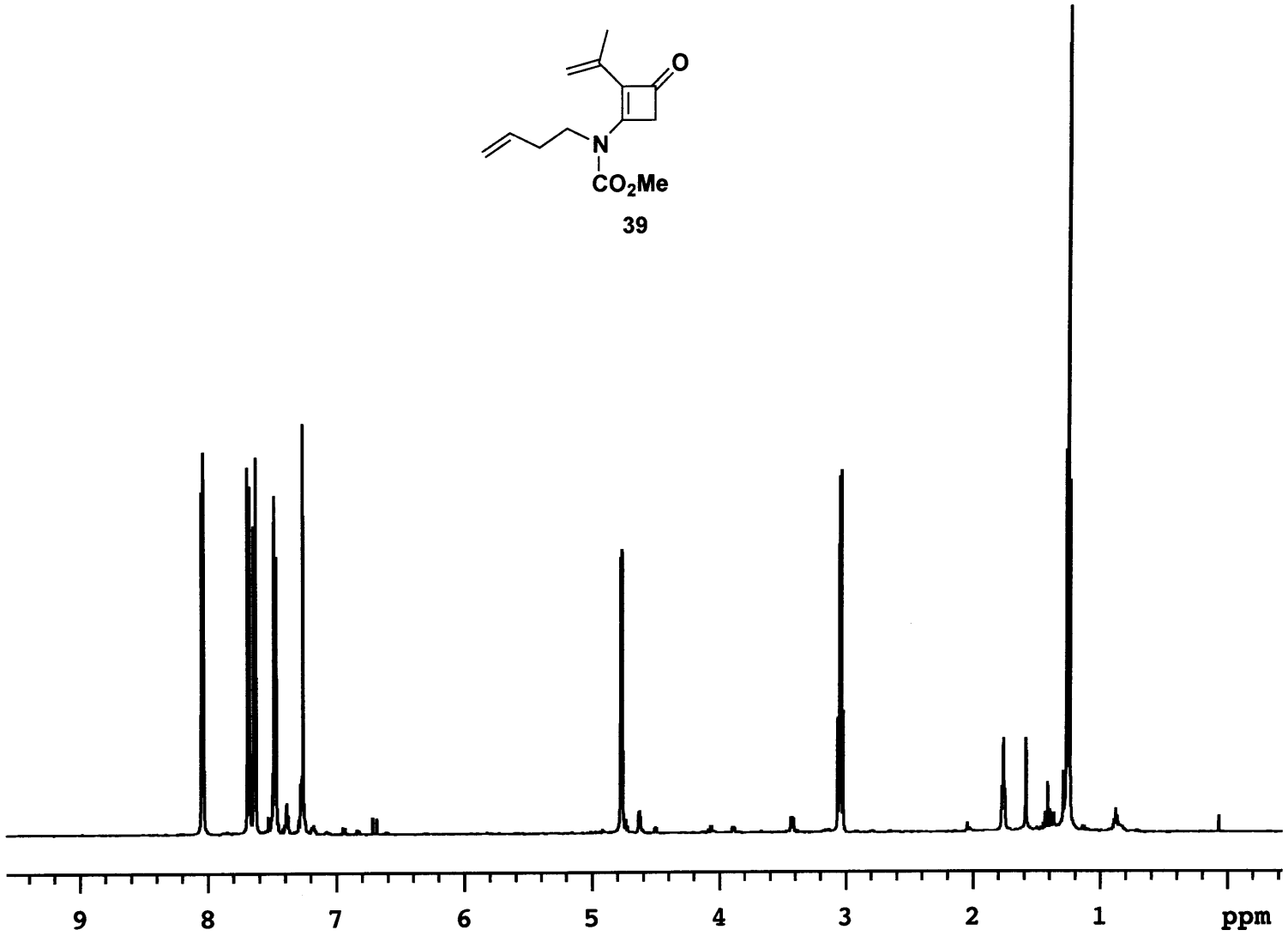


3-[*N*-(3-Butenyl)-*N*-(methoxycarbonyl)amino]-2-isopropenyl-2-cyclobuten-1-one (39).

Reaction of ynamide **31** (0.109 g, 0.564 mmol) with ketene in the absence of solvent for 44 h according to the general procedure provided 0.166 g of dark red oil which was purified by column chromatography on 10 g of silica gel (gradient elution with 0-20% EtOAc-hexanes) to furnish 0.087 g (65%) of **39** as a pale yellow oil: IR (neat) 2958, 1737, 1642, 1595, 1416, 1390, 1368, and 1220 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (m, 1H), 5.17 (quint, J = 1.64 Hz, 1H), 5.08 (m, 1H), 5.06 (m, 1H), 4.90 (m, 1H), 3.89 (m, 1H), 3.86 (s, 3H), 3.51 (s, 2H), 2.34 (m, 2H), and 1.94 (dd, J = 1.53, 1.07 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.8, 157.9, 153.3, 134.6, 133.6, 127.9, 117.9, 117.8, 54.2, 51.1, 46.6, 32.9, and 22.3; HRMS-EI *m/z* $[M]^+$ calcd for $C_{13}H_{17}NO_3$, 236.1281; found 236.1291.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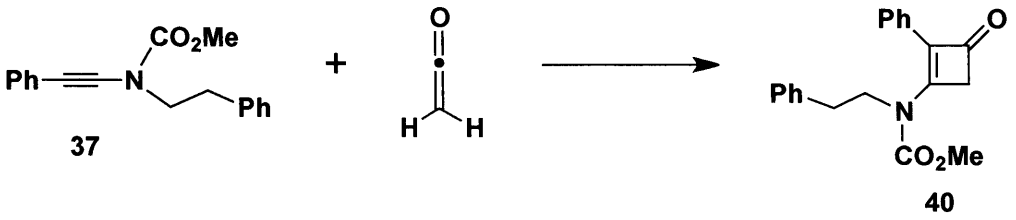
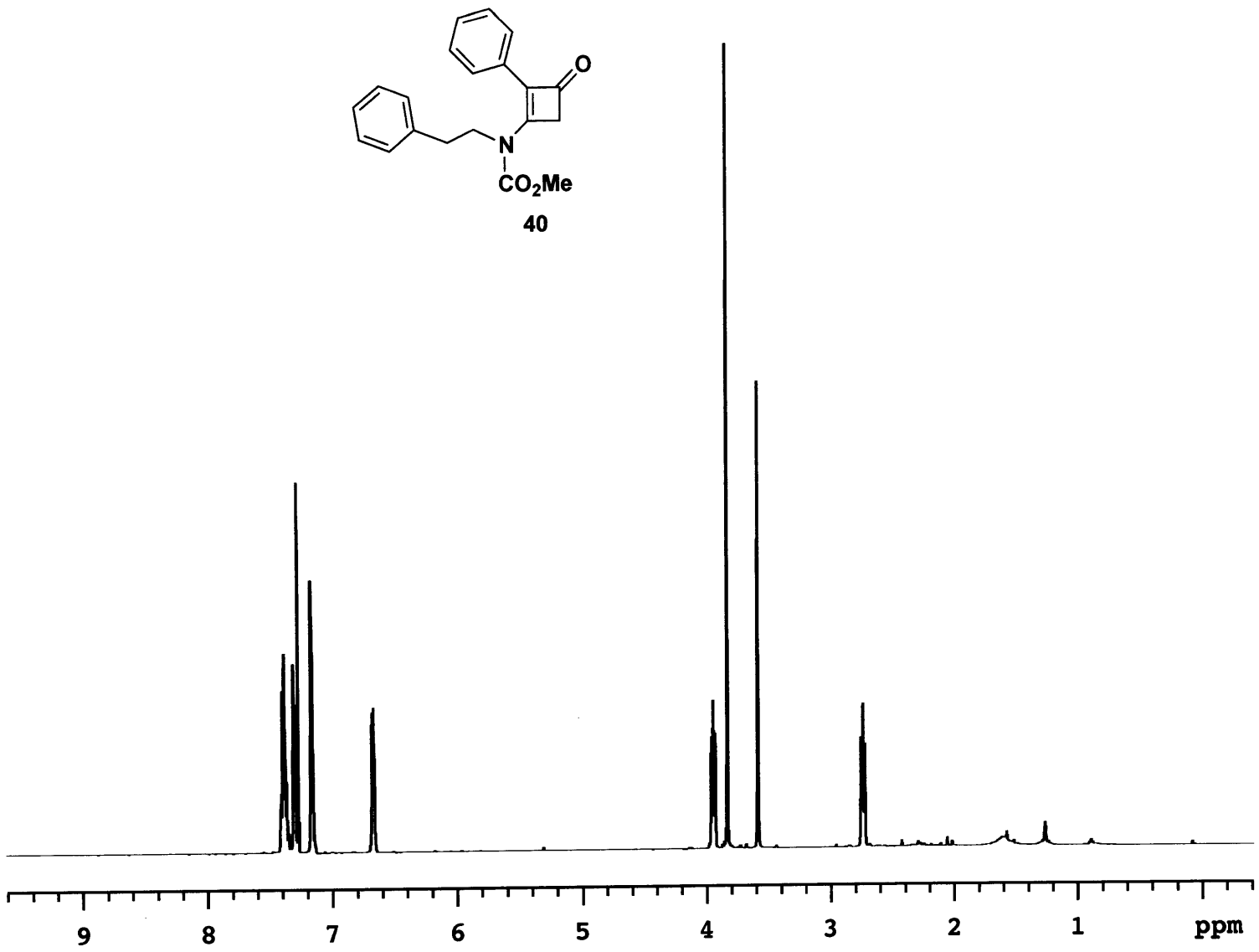


3-[*N*-Methoxycarbonyl-*N*-(2-phenylethyl)amino]-2-phenyl-2-cyclobuten-1-one (40).

Reaction of ynamide **37** (0.100 g, 0.377 mmol) with ketene in the absence of solvent for 42 h according to the general procedure provided 0.125 g of dark red oil which was purified by column chromatography on 6 g of silica gel (gradient elution with 0-20% EtOAc-hexanes) to furnish 0.078 g (67%) of **40** as a pale yellow solid: mp 99-101 °C; IR (CH_2Cl_2) 3028, 2956, 2361, 1749, 1735, 1619, 1590, and 1399 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 3H), 7.31 (app d, J = 0.92 Hz, 2H), 7.16 (t, J = 2.6 Hz, 3H), 6.67 (dd, J = 5.8, 2.4 Hz, 2H), 3.94 (t, J = 7.8 Hz, 2H), 3.83 (s, 3H), 3.59 (s, 2H), and 2.74 (t, J = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 158.8, 153.4, 137.3, 129.6, 129.3, 128.9, 128.7, 128.6, 128.3, 127.0, 126.4, 54.4, 51.8, 49.4, and 34.9; HRMS-EI *m/z* $[M]^+$ calcd for $C_{20}H_{19}NO_3$, 322.1438; found 322.1446.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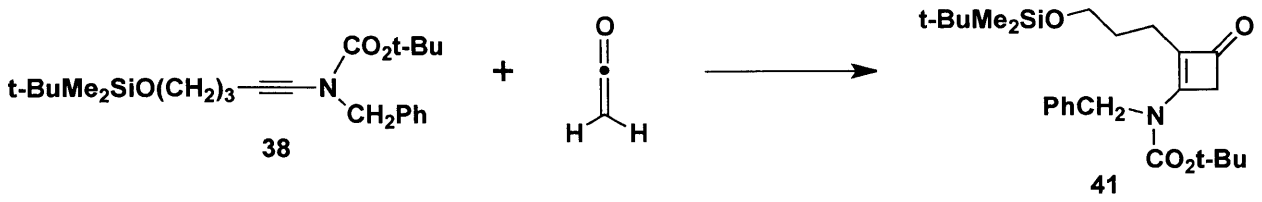
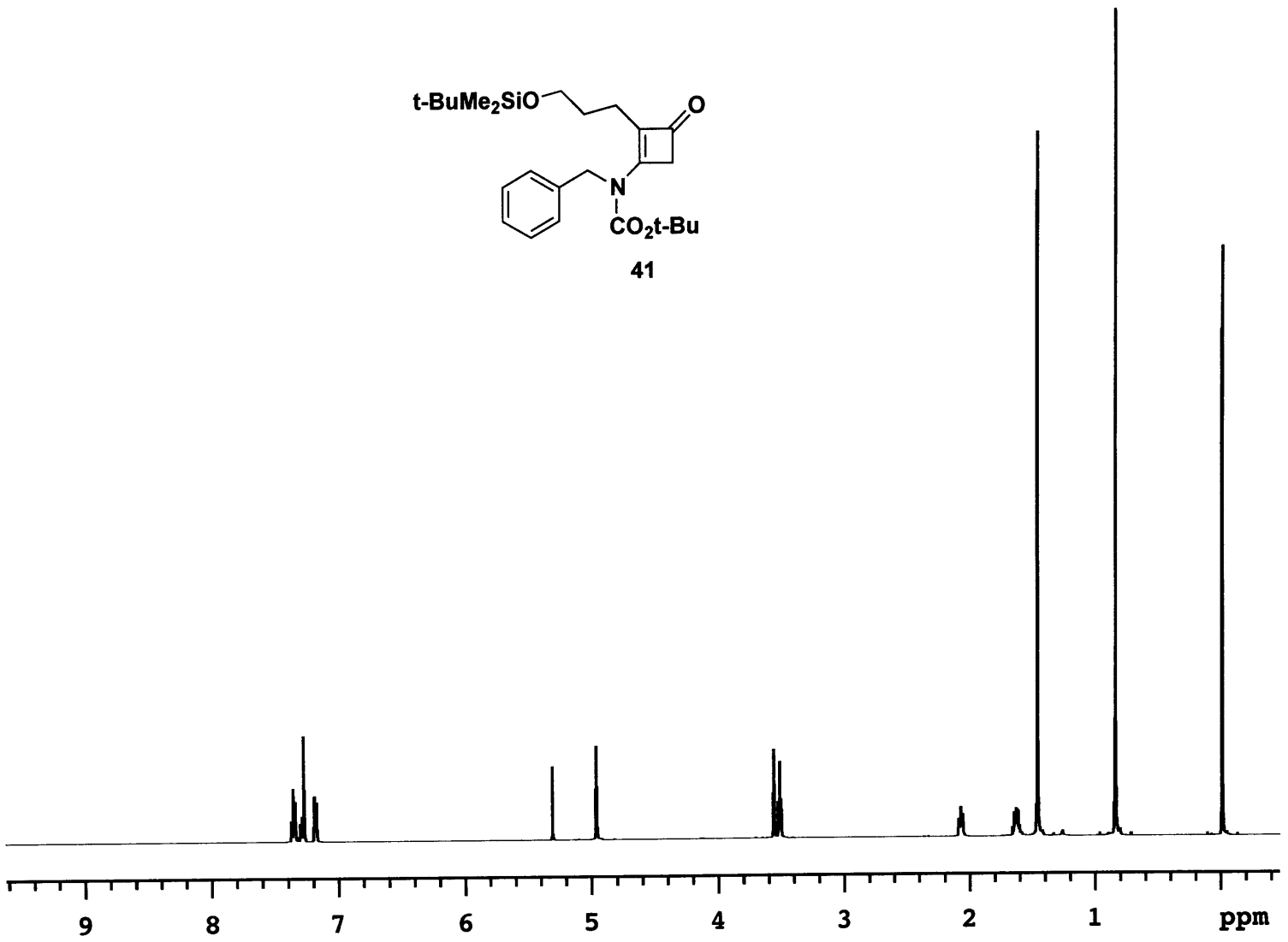
ppm



3-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]-2-(3-*tert*-butyldimethylsiloxybutyl)-2-cyclobuten-1-one (41).

Reaction of ynamide **38** (0.100 g, 0.248 mmol) in 0.5 mL of CH_3CN with ketene for 10 h according to the general procedure provided 0.114 g of dark red oil which was purified by column chromatography on 6 g of silica gel (gradient elution with 0-10% EtOAc-hexanes) to furnish 0.095 g (86%) of **41** as an orange oil: IR (neat) 2955, 2930, 2857, 1756, 1732, 1606, 1370, 1239, and 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (app t, J = 7.4 Hz, 2H), 7.29 (app d, J = 7.3 Hz, 1H), 7.18 (d, J = 7.2 Hz, 2H), 4.96 (s, 2H), 3.56 (t, J = 1.6 Hz, 2H), 3.51 (t, J = 6.1 Hz, 2H), 2.07 (t, J = 7.6 Hz, 2H), 1.63 (m, 2H), 1.46 (s, 9H), 0.84 (s, 9H), and -0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.4, 160.7, 151.5, 137.0, 129.0, 127.7, 126.0, 125.7, 84.3, 62.6, 51.4, 50.9, 31.4, 28.1, 26.1, 20.5, 18.5, and -5.1; HRMS-EI *m/z* $[M]^+$ calcd for $C_{25}H_{39}NO_4Si$, 446.2721; found 446.2737.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ppm