

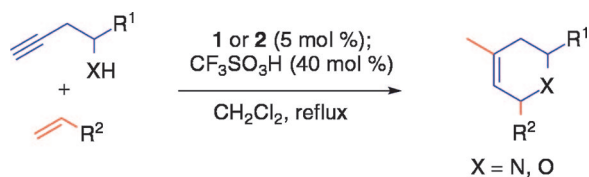
Enyne Metathesis/Brønsted Acid-Promoted Heterocyclization

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Received December 1, 2008



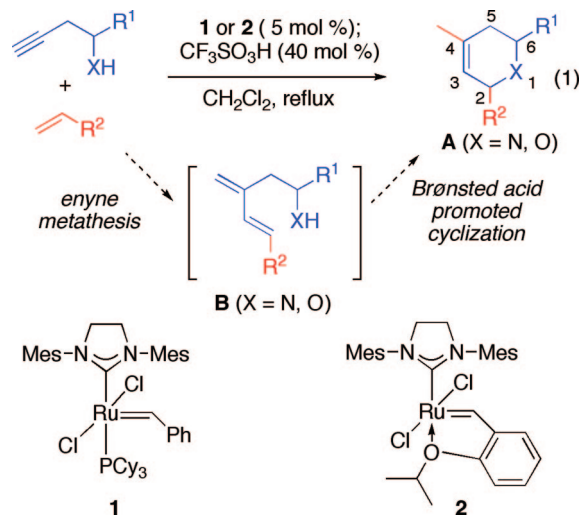
1 = (H₂IMes)(Cy₃P)Cl₂Ru=CHPh, Grubbs' catalyst
2 = (H₂IMes)Cl₂Ru=CHC₆H₄O-*i*-Pr, Hoveyda-Blechert catalyst

The “one-pot” synthesis of nitrogen heterocycles and an oxygen heterocycle by enyne metathesis and *in situ* cyclization is reported.

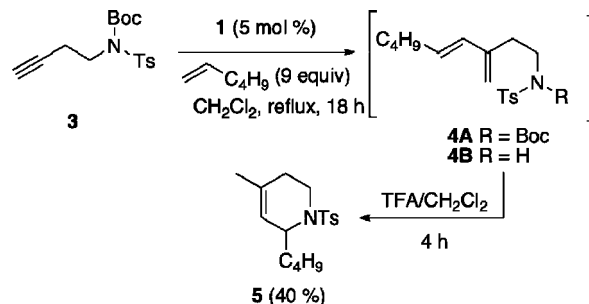
Due to their prominence in pharmaceuticals, heterocycles continue to demand the attention of organic chemists. In particular, rapid access to heterocycles from acyclic precursors (heterocyclization) is an attractive goal. In our investigations directed toward the end functionalization of 1,3-dienes **B** obtained by enyne metathesis, we found that Brønsted acids can be used to effect cyclization of simple diene precursors in a “one-pot” reaction (eq 1 in Scheme 1). The net reaction results in both cyclization and the addition of nitrogen and hydrogen to the ends of the diene, so it can be described as a formal 1,4-hydroamination. In this Note, we show the effectiveness of this reaction as a heterocycle synthesis, for both dehydropiperidines (tetrahydropyridines) and tetrahydropyrans. Since the diene substrates are readily accessible by catalytic enyne metathesis, a facile new route to heterocycle synthesis from alkynes is provided through application of this methodology.

Transition metal-based methods are the most commonly used methods for the cyclization of 1,3-dienes to form heterocycles. Palladium(II) activation of 1,3-dienes results in the formation of both nitrogen^{1a–d} and oxygen^{1e–i} heterocycles through

SCHEME 1. One-Pot Approach to Heterocycles: Enyne Metathesis and Acid-Promoted Cyclization



SCHEME 2. Boc Deprotection Results in Cyclative 1,4-Hydroamination



electrophilic activation (Bäckvall reaction). In these cases, reoxidation of the metal is required. Our group previously showed that the single-step enyne metathesis preparation of 1,3-cyclohexadienes could be efficiently joined with the Bäckvall reaction.² If a hydrogen atom and a nitrogen nucleophile are added to the ends of the diene, then the process is a net 1,4-hydroamination. Intramolecular 1,4-hydroamination of 1,3-dienes has been described by Hong and Marks with use of lanthanide catalysts to prepare pyrrolidines.³ For several years, our research group has been interested in the enyne metathesis as a means to rapidly access 1,3-dienes of varied substitution pattern. As a part of this program, we have been interested in introducing heteroatom functionality contained in the alkene or alkyne substrates. Our investigation was prompted by two research goals: first, to probe the electrophilic reactivity of the 1,3-diene, and second, by our desire for a “one-pot” transformation to access heterocycles. Our study began with electrophilic diene activation by a proton.

Preliminary studies identified an acid-promoted cyclization under conditions of Boc protecting group removal (Scheme 2).

(1) Nitrogen Heterocycles: (a) Bäckvall, J. E.; Nyström, J. E. *J. Chem. Soc., Chem. Commun.* **1981**, 5, 9–61. (b) Bäckvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 3683–3685. (c) Andersson, P. G.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 8696–8698. (d) Riesinger, S. W.; Lofstedt, J.; Pettersson-Fasth, H.; Bäckvall, J.-E. *Eur. J. Org. Chem.* **1999**, 3277–3280. Oxygen heterocycles: (e) Bäckvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 6374–6381. (f) Koroleva, E. B.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 5397–5400. (g) Nilsson, Y. I. M.; Aranyos, A.; Andersson, P. G.; Bäckvall, J.-E.; Parrain, J.-L.; Ploteau, C.; Quintard, J.-P. *J. Org. Chem.* **1996**, *61*, 1825–1829. (h) Itami, K.; Palmgren, A.; Bäckvall, J.-E. *Tetrahedron Lett.* **1998**, *39*, 1223–1226. (i) Verboom, R. C.; Persson, B. A.; Bäckvall, J.-E. *J. Org. Chem.* **2004**, *69*, 3102–3111.

(2) Middleton, M. D.; Peppers, B. P.; Diver, S. T. *Tetrahedron* **2006**, *62*, 10528–10540.

(3) (a) Hong, S.; Marks, T. J. *J. Am. Chem. Soc.* **2002**, *124*, 7886–7887. (b) Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 15878–15892.

TABLE 1. Acid Screening

| entry | acid | equiv | time, h | conversion, ^a % | yield of 5, ^b % |
|-------|---------------------|-------|---------|----------------------------|----------------------------|
| 1 | TFA | 9.0 | 1 | 100 | 81 |
| 2 | HCl | 0.4 | 5 | 59 | ND |
| 3 | CSA | 0.4 | 5 | 78 | ND |
| 4 | MeSO ₃ H | 0.4 | 5 | 100 | 67 |
| 5 | TfOH | 0.4 | 1 | 100 | 83 |

^a Conversion determined by gc. ^b Isolated yield. ND = not determined.

Exposure of diene *E*-4A⁴ to TFA/CH₂Cl₂ resulted in cyclization with concurrent Boc protecting group removal. In the event, excess TFA gave clean conversion to the nitrogen heterocycle 5, with no other products detected by tlc.

Having identified a simple acid-catalyzed cyclization of the 1,3-diene, we next investigated other Brønsted acids. These studies were conducted as one-pot sequential tandem reactions, using the diene generated in situ by enyne metathesis.⁵ Once the metathesis was complete, the mixture of the 1,3-diene, excess 1-hexene, and Grubbs catalyst 1 was directly treated with the indicated amount of acid and heating was continued at 40 °C (Table 1). Excellent conversion and very good chemical yield was obtained with a large excess of trifluoroacetic acid (TFA, p*K*_a 3.45 in DMSO). Other strong acids were screened to decrease the amount of acid needed for cyclization. Anhydrous HCl (p*K*_a 1.8 in DMSO) gave incomplete conversion, possibly due to loss of HCl over the protracted period of heating (entry 2). The organic-soluble camphorsulfonic acid (CSA) proved effective in substoichiometric amount, though only 78% conversion was found at 5 h reaction time (entry 3). Methanesulfonic acid (p*K*_a 1.6 in DMSO) gave higher conversion and a moderate isolated yield. The disagreement between the conversion and isolated yield is likely due to competing cationic polymerization of the 1,3-diene during the extended reaction time. Last, 40 mol % of triflic acid (p*K*_a 0.3 in DMSO) was found to give good conversions and high chemical yield of the cyclization product (entry 5). The conditions in entry 5 were adopted as the standard conditions. Triflic acid has been used to promote the intramolecular hydroamination and hydroalkoxylation of alkenes by Hartwig and co-workers.⁶ Triflic acid has also recently been used by He and co-workers to effect an intermolecular 1,4-hydroamination of 1,3-dienes employing carbamate nucleophiles.^{7,8} In the present study, very strong Brønsted acids were found to promote the cyclization at substoichiometric amounts on the crude intermediate diene obtained through enyne metathesis.

The one-pot enyne metathesis/heterocyclization was conducted with catalytic triflic acid. The results are summarized in

TABLE 2. Nitrogen Heterocycles by the One-Pot Cyclization Approach^a

| Entry | Alkyne | Alkene | Product |
|-------------|--------|---------------------------------|--|
| 1 2 | | 1-hexene ethylene | 5 (R ₁ =C ₄ H ₉ , 83%) 7 (R ₁ =H, 52%) |
| 3 4 5 | | 1-hexene propene ethylene | 9 (R ₁ =C ₄ H ₉ , 65%) 10 (R ₁ =CH ₃ , 76%) 11 (R ₁ =H, 75%) |
| 6 | | 1-hexene | 13 (73%) |
| 7 8 | | 1-hexene ethylene | 15 (R ₁ =C ₄ H ₉ , 67%) 16 (R ₁ =H, 66%) |

^a Reaction conditions: 1 (7–8 mol %), 1-hexene (9 equiv), CH₂Cl₂, reflux, 1 h; addition of TfOH (0.4 equiv), reflux, 1 h. The ethylene and propene runs were conducted for a period of 18 h with 5–10 mol % of 1 at room temperature, followed by addition of TfOH and reflux, 1 h.

Table 2. For the metathesis step, the 1-hexene runs were conducted at 40 °C over 1 h; the ethylene runs were conducted at rt over 18 h at 60–90 psig in a pressure tube. At the conclusion of the metathesis, 40 mol % of triflic acid (TfOH) was introduced and the reaction was stirred for 1 h. In this way, the resulting heterocycle was obtained in 83% and 52% yield (entries 1,2). α -Substitution adjacent to the nitrogen atom was tolerated, and in the cases of hexene and propene (entries 3 and 4), 2,6-disubstituted dehydropiperidines were formed as single diastereomers. For example, in the crude ¹H NMR spectrum of 9, one diastereomer was observed with no other diastereomer seen within the limits of NMR detection.⁹ In the ethylene case, the reaction proceeded with similar yield (entry 5). The chiral propargyl amino acid derivative 12 underwent tandem reaction to afford the Fmoc-protected nitrogen heterocycle with 2,6-disubstitution (entry 6). Last, the *p*-nosyl protecting group could be employed in the sequence, giving the corresponding nitrogen heterocycles (entries 7 and 8) in yields comparable to that obtained with the tosyl group.

The relative stereochemistry of the 2,6-disubstituted heterocycles was established by structural studies on dehydropiperidine

(4) In this case, only *E*-4A was detected. In the cross metathesis step with simple alkenes, longer periods of heating give primarily the *E*-isomer: (a) Giessert, A. J.; Diver, S. T. *J. Org. Chem.* **2005**, *70*, 1046–1049. (b) Clark, D. A.; Kulkarni, A. A.; Kalbarczyk, K.; Schertzer, B.; Diver, S. T. *J. Am. Chem. Soc.* **2006**, *128*, 15632–15636.

(5) Similar studies were conducted with pure, *E*-4B: 4 equiv TFA promoted the cyclization (100% conversion, 73% isolated). However, in the one-pot reaction, 4 equiv of TFA did not result in full conversion of the intermediate 1,3-diene. Since excess alkene was still present, higher amounts of acid were needed, see ref 8.

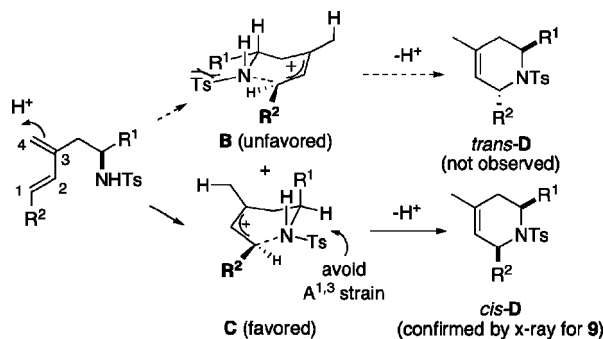
(6) (a) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471–1474. (b) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179–4182.

(7) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich Nicholas, W.; He, C. *Org. Lett.* **2006**, *8*, 4175–4178.

(8) Interestingly, the He study (ref 7) reported intermolecular 1,2-hydroamination of unactivated alkenes. In the present case, it is likely that some loss of material is due to addition reactions to remaining 1-hexene.

(9) See the Supporting Information.

SCHEME 3. Rationale for the Observed Selectivity



9.⁹ Slow crystallization of **9** from ethanol produced X-ray quality crystals, mp 93–95 °C. The *n*-butyl group and the phenyl moiety were found to be *cis*-oriented, with the tosyl group occupying the opposite side of the ring. On the basis of these data, we have assigned the 2,6-*cis* relative stereochemistry in disubstituted heterocycles **10** and **13**. The observation of an axial arrangement of the substituents at the 2- and 6-position, along with an axial *p*-tosyl group, is consistent with observations made by others.¹⁰

The rationale for selective formation of diastereomer *cis*-**9** is presented in Scheme 3. Protonation at C4 would produce an allylic carbocation that could undergo nucleophilic attack by the nitrogen from either face, giving **B** and **C**. In **B**, the required conformation adopted during C–N bonding positions the tosyl group to develop strain with the R¹ group. Alternatively, attack on the other face of the allylic carbocation via **C** alleviates the A^{1,3}-like strain arising from the tosyl group and R¹ in conformation **B**, thereby giving rise to diastereomer *cis*-**D**.^{10,11}

The present method is distinct from metathesis methods used for heterocyclic ring synthesis. There are many examples of metathesis-based approaches to nitrogen heterocycles.¹² In terms of recent developments, the exchange of a carbocycle for the heterocycle by ring rearrangement can be found in the independent studies of Blechert¹³ and Mori.¹⁴ Metathesis-based methods form the heterocyclic ring through C–C bond formation: for product **A**, the C₃–C₄ bond would be constructed by ring-closing metathesis (Scheme 1). In this work, the enyne metathesis is instead used to assemble the 1,3-diene for electrophilic activation. In structure **A** (X = N), the enyne metathesis formally makes the C₂–C₃ and C₄–C₅ bond, whereas the heterocycle is formed by C–N bonding promoted by the Brønsted acid catalyst. As a result, the use of the enyne metathesis/acid-promoted cyclization offers an alternative bond connection to heterocycle synthesis. Importantly, the R¹ and R² elements are combined in an additive way from the respective alkene and alkyne reactants.

(10) (a) Hedley, S. J.; Moran, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harriy, J. P. A. *Synlett* **2001**, 10, 1596–1598. (b) Hersh, W. H.; Xu, P.; Simpson, C. K.; Grob, J.; Bickford, B.; Hamdani, M. S.; Wood, T.; Rheingold, A. L. *J. Org. Chem.* **2004**, 69, 2153–2163.

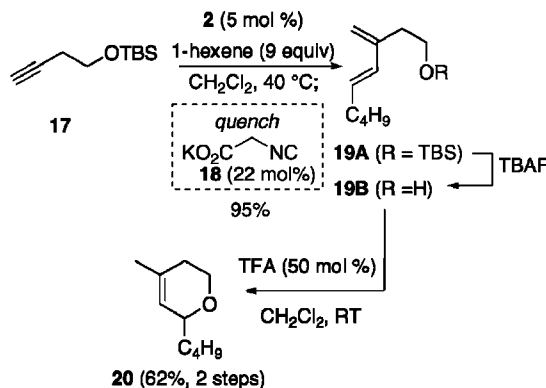
(11) A^{1,3} strain was invoked in *N*-acyl piperidinone to explain diastereoselection during conjugate addition reactions: (a) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Org.* **1988**, 110, 7445–7447. For similar reasons, the *N*-tosyl group in a piperidine ring system causes the 2-substituent to occupy an axial position. See: (b) Craig, D. L.; McCague, R.; Potter, G.; Williams, M. R. V. *Synlett* **1998**, 55–57, and ref 10.

(12) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, 104, 2199–2238.

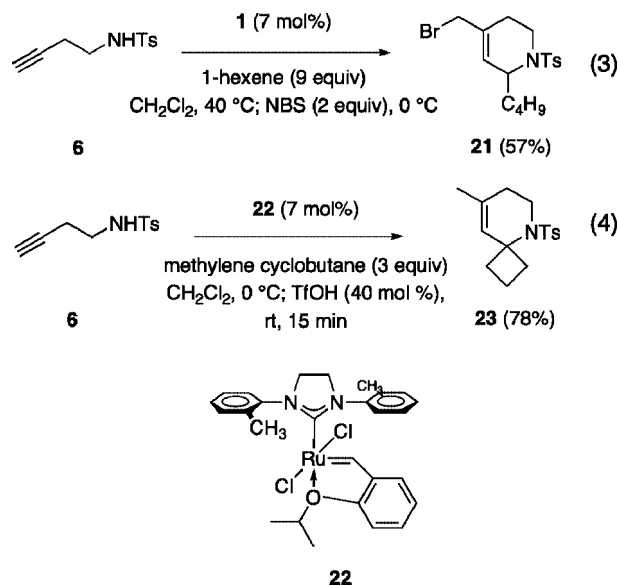
(13) Piperidine: (a) Voigtmann, U.; Blechert, S. *Synthesis* **2000**, 893–898. Other ring-rearrangements: (b) Randl, S.; Lucas, N.; Connon, S. J.; Blechert, S. *Adv. Synth. Cat.* **2002**, 344, 631–633. (c) Imhof, S.; Blechert, S. *Synlett* **2003**, 609–614. (d) Boehrsh, V.; Neidhoefer, J.; Blechert, S. *Angew. Chem., Int. Ed.* **2006**, 45, 1302–1305.

(14) Kitamura, T.; Mori, M. *Org. Lett.* **2001**, 3, 1161–1163.

SCHEME 4. Formation of an Oxygen Heterocycle



SCHEME 5. NBS Electrophilic Activation (Eq 3) and Spirocycle Formation (Eq 4)



The enyne metathesis/cyclization also provides tetrahydropyrans by a similar 1,4-addition with use of substoichiometric TFA (Scheme 4).¹⁵ In this case, additional steps are required to protect the alcohol during the metathesis. Attempts to use the free homopropargylic alcohols under standard enyne metathesis conditions gave trace amounts of the conjugated dienes. As a result, the alcohol was protected as the TBS ether. At the conclusion of the metathesis, the Grubbs ruthenium carbene was quenched¹⁶ by the addition of the polar isocyanide **18**, and the diene **19** isolated by chromatography. Deprotection of the TBS group and cyclization with TFA gave the 2-substituted tetrahydropyran **20** in good yield (62%, two steps).

The cyclization could be induced by other electrophiles. Position-selective activation of the 1,3-diene could be achieved through bromonium ion formation (NBS). Intramolecular attack by the nitrogen nucleophile and subsequent loss of proton provides the 1,4-difunctionalized product **21** in good isolated yield (eq 3, Scheme 5). The allylic bromide provides further options for elaboration of dehydropiperidine **21** through C–C bond formation. This electrophilic activation provides a means

(15) In this case, fewer equivalents of TFA were found to promote the cyclization. Carbene **1** also promoted this metathesis.

(16) Galan, B. R.; Kalbarczyk, K. P.; Szczepankiewicz, S.; Keister, J. B.; Diver, S. T. *Org. Lett.* **2007**, 9, 1203–1206.

to functionalize the allylic methyl group found in the products of Table 2, above.

Making use of our recent cross metathesis method permitted access to a spiro-fused dehydropiperidine. For access to the spirocycle **23**, we required disubstitution on the terminal position of the 1,3-diene, which is normally difficult to achieve in cross metathesis. Use of the geminally-substituted alkene methylene cyclobutane¹⁷ gave rise to the novel spirocyclic heterocycle **23** (eq 4, Scheme 5). For this metathesis, a specialized Grubbs catalyst **22**¹⁸ was used so the metathesis could be conducted at low temperature. The Brønsted acid-promoted cyclization proved to be very fast, with complete reaction occurring within 15 min at rt (eq 4, Scheme 5).

In summary, a new one-pot enyne metathesis, acid-promoted cyclization has been developed. The reaction represents an efficient means of heterocycle synthesis through the acid-promoted end functionalization of an acyclic diene. This process is very simple and uses readily available and inexpensive Brønsted acids. In the case of dehydropiperidine heterocycle synthesis, the reaction proceeds with high diastereoselectivity. Further studies directed toward electrophilic activation to form a variety of heterocyclic rings are ongoing in our laboratories.

Experimental Section⁹

General Procedure for Heterocycle Formation. To a dry 50 mL Schlenk tube was added a solution of alkyne (0.5 mmol) and 1-hexene (4.5 mmol, 9 equiv) in 10 mL of dichloromethane (0.05 M). The reaction vessel was then placed in a preheated oil bath at 45 °C. Grubbs' catalyst **1** (0.035 mmol, 30 mg) was added and the reaction mixture was allowed to stir until complete consumption of alkyne, as detected by TLC analysis. At this time, approximately 180 μ L (0.2 mmol) of a 1.13 M TfOH solution in dichloromethane was added and the reaction was allowed to stir until consumption of the intermediate 1,3-diene was complete, then the crude mixture was concentrated in vacuo (rotary evaporator) to give the crude products as oils.

6-Butyl-4-methyl-1-tosyl-1,2,3,6-tetrahydropyridine (5). Following the general procedure, the crude mixture was purified by flash column chromatography with silica gel (1:6 ethyl acetate:

petroleum ether) affording 115 mg of **5** as a clear colorless amorphous solid in 83% yield. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.34 (d, *J* = 1.5 Hz, 1H), 4.24 (d, *J* = 1.5 Hz, 1H), 3.82 (dd, *J* = 14.5, 6.5 Hz, 1H), 3.13 (ddd, *J* = 14.5, 12.0, 4.5 Hz, 1H), 2.41 (s, 3H), 1.74–1.66 (m, 1H), 1.59 (m, 3H), 1.50 (s, 3H), 1.42–1.28 (m, 4H), 0.89 (t, 7.5 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃, ppm) δ 142.8, 138.7, 132.2, 129.3, 127.0, 122.0, 53.7, 38.5, 34.9, 28.3, 27.7, 23.2, 22.6, 21.4, 14.0; FT-IR (CH₂Cl₂, cm⁻¹) 3026, 2967, 2921, 2861, 2730, 1920, 1683, 1604, 1499, 1453, 1387, 1348, 1229, 1157, 1104, 1045, 953, 900, 815, 775, 690, 637; ESI-MS molecular ion calculated for C₁₇H₂₅O₂NS 307.1606, found 308.1671 (*M* + 1), error -2.5 ppm.

6-Butyl-4-methyl-2-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine (9). Following the general procedure, **9** was obtained with use of alkyne **8** (424 mg, 1.42 mmol) and 1-hexene (1.58 mL, 12.8 mmol) in 28 mL of dichloromethane (0.05 M). After removal of the solvent, **9** was obtained as a crude yellow solid. The solid was recrystallized by slow evaporation with ethanol affording 335 mg of a white solid, mp 93–95 °C, in 65% yield. Crystals from this sample were submitted for single crystal X-ray structure determination.⁹ Analytical TLC *R_f* 0.42 (1:4 ethyl acetate: hexanes); ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 4H), 7.23 (t, *J* = 7.5 Hz, 1H), 5.35 (s, 1H), 5.24 (br d, *J* = 7.0 Hz, 1H), 4.27 (br s, 1H), 2.43 (s, 3H), 2.20 (d, *J* = 17.5 Hz, 1H), 1.81 (dt, *J* = 17.5, 3.0 Hz, 1H), 1.70 (s, 3H), 1.22–1.15 (m, 2H), 1.05–0.93 (m, 2H), 0.86–0.77 (m, 2H), 0.70 (d, *J* = 7.5 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃, ppm) δ 142.9, 140.7, 138.3, 129.5, 129.4, 128.0, 127.2, 127.0, 122.1, 54.4, 51.7, 35.2, 28.6, 28.2, 23.3, 22.3, 21.5, 13.8; FT-IR (CH₂Cl₂, cm⁻¹) 2967, 2927, 2861, 1598, 1493, 1460, 1387, 1341, 1282, 1157, 1098, 1045, 1012, 933, 887, 815, 690; ESI-MS molecular ion calculated for C₂₃H₂₉O₂NS 383.1914, found 406.1802 (*M* + Na), error -2.3.

Acknowledgment. The authors thank Dr. Mateusz Pitak (SUNY Buffalo) for obtaining the X-ray structure of **9** and William Karnofel for his assistance in the preparation of this manuscript. This work was partially supported by the Petroleum Research Fund (PRF AC-44202) and the NSF (CHE-601206).

Supporting Information Available: Experimental procedures and full characterization data for new compounds as well as detailed crystallographic data for compound **9**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO802582K

(17) Use of methylene cyclobutane in enyne metathesis: Clark, D. C.; Karnofel, W.; Basile, B.; Diver, S. T. *Org. Lett.* **2008**, *10*, 4927–4929.

(18) (a) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrod, Y. *Org. Lett.* **2007**, *9*, 1589–1592. (b) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444.