JOC Note

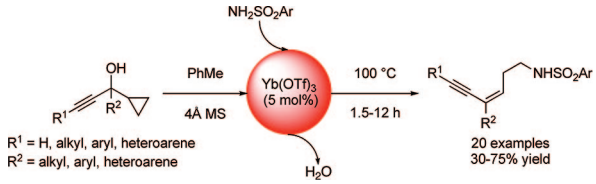
Ytterbium(III) Triflate-Catalyzed Amination of 1-Cyclopropylprop-2-yn-1-ols as an Expedient Route to Conjugated Enynes

Weidong Rao, Xiaoxiang Zhang, Ella Min Ling Sze, and Philip Wai Hong Chan*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

waihong@ntu.edu.sg

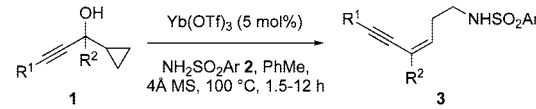
Received November 4, 2008



Ytterbium(III) triflate-catalyzed ring opening of substituted 1-cyclopropyl-2-propyn-1-ols with sulfonamides as an efficient synthetic route to conjugated enynes is described herein. The reaction was operationally straightforward and accomplished in moderate to good yields and regioselective manner in all except one case under mild conditions.

Establishing methods to conjugated enynes is currently an active area in organic synthesis due to their frequent use as building blocks in numerous strategies to compounds of biological and material interest.[1] While this has led to a myriad of works devoted to this reaction, the number of methods that can install this unsaturated hydrocarbon moiety without competitive formation of undesired regio- and stereoisomers has remained sparse.[1,2] For this reason, the development of new synthetic routes to conjugated enynes in an efficient and stereoselective manner continues to be actively pursued. In a recent notable advance, Nishibayashi and co-workers demonstrated that *trans*-substituted conjugated enynes could be obtained from regioselective diruthenium-catalyzed ring opening of terminal 1-cyclopropyl-2-propyn-1-ols with aniline.[3] Following this seminal work, we[4] and Liang[5] showed this atom-economical ring opening process, which produces H_2O as potentially the only byproduct, to be applicable to a variety of substituted 1-cyclopropyl-2-propyn-1-ols and sulfonamide and alcohol nucleophiles using gold catalysis. However, this method would also greatly benefit from the use of cheaper and commercially available catalysts, such as lanthanide complexes. To our knowledge, synthetic approaches that explore combining rare earth metals as strong Lewis acid catalysts[6] with alcohol pro-electrophiles[7] have thus far been limited to benzylation and allylation of aromatic and 1,3-dicarbonyl compounds with benzylic and allylic alcohols.[8] As part of an ongoing program examining the utility of alcohols as building blocks in organic synthesis,[4,9] we report in this Note the use of $Yb(OTf)_3$ for ring opening of substituted 1-cyclopropyl-2-propyn-1-ols with sulfonamides (Scheme 1). The conjugated enyne products were afforded in yields and regioselective manner comparable to those reported for the closely related Ru_2- or Au-promoted approaches to this synthetically useful building block.

SCHEME 1. Regioselective $Yb(OTf)_3$-Catalyzed Formation of Conjugated Enynes from Cyclopropylprop-2-yn-1-ols



R^1 = H, alkyl, aryl, heteroarene
R^2 = alkyl, aryl, heteroarene

Initially, we chose to focus our attentions on the nucleophilic ring opening of 1-cyclopropyl-1,3-diphenylprop-2-yn-1-ol **1a** with *p*-toluenesulfonamide ($TsNH_2$) **2a** by a variety of Lewis and Brønsted acid catalysts to establish the reaction conditions (Table 1). This revealed that treating a toluene solution containing 1 equiv of **1a** and 2 equiv of **2a** with 5 mol % of $Yb(OTf)_3$ at 100 °C for 5 h gave the best result (entry 1). Under these conditions, (*Z*)-*N*-(4,6-diphenylhex-3-en-5-ynyl)-4-methylbenzenesulfonamide **3a** was afforded in 75% yield, compa-

(1) For recent reviews, see: (a) Shirtcliff, L. D.; McClintock, S. P.; Haley, M. M. *Chem. Soc. Rev.* **2008**, *37*, 343. (b) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (c) Zeni, G.; Braga, A. L.; Stefani, H. A. *Acc. Chem. Res.* **2003**, *36*, 731.

(2) For recent examples, see: (a) Liu, Y.; Nishiura, M.; Wang, Y.; Hou, Z. *J. Am. Chem. Soc.* **2006**, *128*, 5592. (b) Zhang, L.-M.; Wang, S.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 1442. (c) Pahadi, N. K.; Camacho, D. H.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 1152. (d) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130.

(3) Yamauchi, Y.; Onodera, G.; Sakata, K.; Yuki, M.; Miyake, Y.; Uemura, S.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 5175.

(4) Rao, W.; Chan, P. W. H. *Chem.—Eur. J.* **2008**, *14*, 10486.

(5) Xiao, H.-Q.; Shu, X.-Z.; Ji, K.-G.; Qi, C.-Z.; Liang, Y.-M. *New J. Chem.* **2007**, *31*, 2041.

(6) For recent reviews, see: (a) Itsuno, S. Polymer-Supported Metal Lewis Acids. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2000; Vol. 2, p 945. (b) Shihasaki, M.; Yarnada, K.-I.; Yoshikawa, N. Lanthanide Lewis Acids Catalysis. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2000; Vol. 2, p 911. (c) Kobayashi, S. Sc(III) Lewis Acids. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2000; Vol. 2, p 883. (d) *Carbocation Chemistry*; Olah, G. A., Prakash, G. K. S., Eds.; John Wiley & Sons: New York, 2004. (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (f) Kagan, H. B. *Chem. Rev.* **2002**, *102*, 1805.

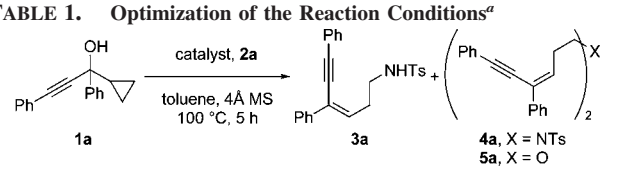
(7) For recent reviews on the use of alcohols as pro-electrophiles, see: (a) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (b) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (c) Muzart, J. *Eur. J. Org. Chem.* **2007**, 3077. (d) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647.

(8) (a) Noji, M.; Konno, Y.; Ishii, K. *J. Org. Chem.* **2007**, *72*, 5161. (b) Huang, W.; Wang, J.; Shen, Q.; Zhou, X. *Tetrahedron Lett.* **2007**, *48*, 3969. (c) Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S. *J. Org. Chem.* **1997**, *62*, 6997. (d) Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S. *Synlett* **1996**, 557.

(9) (a) Zhang, X.; Rao, W.; Chan, P. W. H. *Synlett* **2008**, Special Issue, 2204. (b) Rao, W.; Chan, P. W. H. *Org. Biomol. Chem.* **2008**, *6*, 2426. (c) Wu, W.; Rao, W.; Er, Y. Q.; Loh, K. J.; Poh, C. Y.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 2620; *Tetrahedron Lett.* **2008**, *49*, 4981. (d) Chang, J. W. W.; Chee, S.; Mak, S.; Buranaprasertsuk, P.; Chavasiri, W.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 2018. (e) Rao, W.; Tay, A. H. L.; Goh, P. J.; Choy, J. M. L.; Ke, J. K.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 122; *Tetrahedron Lett.* **2008**, *49*, 5112.

10.1021/jo8024626 CCC: $40.75
Published on Web 01/07/2009

TABLE 1. Optimization of the Reaction Conditions[a]



			yield (%)		
entry	catalyst	solvent	**3a**	**4a**	**5a**
1	$Yb(OTf)_3$	PhMe	75	*b*	*b*
2[c]	$Yb(OTf)_3$	PhMe	53	15	12
3	$Yb(OTf)_3$	1,2-dichloroethane	55	–	28
4	$Yb(OTf)_3$	MeCN	*b*	–	–
5	$Yb(OTf)_3$	THF	*b*	–	–
6	$Cu(OTf)_2$	PhMe	54	–	6
7	AgOTf	PhMe	39	6	*b*
8	$InCl_3$	PhMe	*d*	–	–
9	$FeCl_3 \cdot 6H_2O$	PhMe	*d*	–	–
10	$TsOH \cdot H_2O$	PhMe	*d*	–	–
11	TfOH	PhMe	23	3	–

[a] All reactions were performed at 100 °C for 5 h with catalyst/**1a**/**2a** ratio of 1:20:40. [b] Trace amount of compound isolated after flash column chromatography. [c] Reaction conducted with 1 equiv of **2a**. [d] No reaction.

rable to those obtained for the closely related Ru_2- and Au-catalyzed reactions with terminal or activated starting alcohols.[3,5] The *cis*-stereochemistry of the conjugated enyne product was confirmed by comparison with NOE spectroscopic data of closely related adducts (see below) and reported literature values.[3,5] In our hands, the dimeric byproducts **4a** and **5a** were also isolated in trace amounts. In contrast, a lower product yield along with significantly higher amounts of the dimeric byproduct was obtained by repeating the reaction with 1 equiv of **2** (entry 2). Similarly, performing the reaction in other solvents was found to be less effective (entries 3−5). When 1,2-dichloroethane was employed as the solvent, a lower product yield of 55% along with **5a** in a higher yield of 28% was obtained (entry 3). On the other hand, TLC and ^{1}H NMR analysis of crude mixtures of reactions conducted in either MeCN or THF detected only the starting alcohol and sulfonamide, which were recovered in near quantitative yields (entries 4 and 5). An inspection of entries 6−11 in Table 1 also revealed the reaction proceeded less well with other common and commercially available Lewis and Brønsted acid catalysts. In these latter reactions, the use of $Cu(OTf)_2$ and AgOTf and TfOH resulted in the formation of **3a** in markedly lower yields along with slightly higher yields of either or both **4a** and **5a** (entries 6 and 7). However, switching the catalyst to $InCl_3$, $FeCl_3 \cdot 6H_2O$, or $TsOH \cdot H_2O$ was found to result in no reaction observed on the basis of TLC analysis (entries 8−10). A low product yield of 23% obtained for the analogous TfOH-mediated reaction also provided evidence that, in the presence of potentially TfOH, the cationic Yb(III) complex is the catalytically active species (entry 11).

To define the scope of the present procedure, we next turned our attentions to the reactions of a variety of unactivated 1-cyclopropyl-2-propyn-1-ols with **2a** (Table 2). Reactions of substituted 1-cyclopropyl-2-propyn-1-ols containing a pendant electron-withdrawing group on the carbinol carbon with **2a** gave the corresponding conjugated enyne products **3b**−**d** in yields of 67−70% (entries 1−3). Similarly, the analogous reaction of **1e**, which contains electron-donating groups at both the alkyne and carbinol carbon centers, with **2a** affords the corresponding product **3e** in 56% yield (entry 4). Likewise, the substituted 1-cyclopropyl-2-propyn-1-ol **1f** bearing a sterically bulky naphthylene group was found to proceed well and afford **3f** in a good yield (entry 5). The present procedure was also shown to work well for 1-cyclopropyl-2-propyn-1-ols containing alkyl and aryl substituent combinations, giving **3h** and **3j**−**l** in 55−73% yield (entries 7 and 9−11). However, moderate yields were obtained for reactions with alcohols containing a cyclopropane group on the alkyne moiety or a terminal acetylene group as in **1g** and **1i** (entries 6 and 8). On the other hand, starting alcohols with pendant thiophene functionalities provided the corresponding conjugated enyne products in good yields (entries 12−14). This is noteworthy as such aromatic ring structures are commonly found in a myriad of bioactive natural and pharmaceutical compounds.[10] Under the standard conditions, reaction of **1p** with **2a** was the only case that was found to be ineffective, giving no product formation based on TLC and ^{1}H NMR analysis and recovery of the starting alcohol in near quantitative yield (entry 15).

Depending on the nature of the substituent on the carbinol carbon of the alcohol substrate, the products shown in Table 2 were exclusively obtained as either the *Z*-isomer for alkyl or aryl groups on the carbinol carbon in all except one case. Similarly, the *E*-product was furnished for heteroarene groups on the carbinol carbon.[11] The *trans*-stereochemistry in **3e** and **3g** and *cis*-stereochemistry in **3m** were also confirmed by NOE analysis (see Supporting Information for details). Reaction of **1l** was the only instance in which the corresponding enyne adduct was obtained as a mixture of *Z* and *E* isomers in a ratio of *Z*/*E* = 83:17 (entry 11). A similar effect of a bulky substituent at the carbinol carbon of the substrate on product regioselectivity has also been reported in the analogous Ru_2- and Au-mediated approaches.[3,5]

To further explore the scope of the $Yb(OTf)_3$-catalzyed reactions, the ring opening of **1a** with a variety of different nitrogen nucleophiles was examined (Table 3). Under the standard conditions, reaction of **1a** with benzenesulfonamide **2b** afforded **3q** in 60% yield (entry 1). Under similar conditions, arylsulfonamides **2c** and **2d**, which contain either a *para*-substituted electron-donating or electron-withdrawing group, respectively, were found to be good nitrogen sources, giving the corresponding conjugated enynes **3r** and **3s** in yields of 69−80% (entries 2 and 3). In contrast, other nitrogen sources such as aniline **2e**, *tert*-butyl carbamate **2f**, and *N*-aminophthalimide **2g** were found to be less effective (entries 4−6). When aniline **2e** was employed as the nucleophile, the reaction was found to proceed to give **3t** in 31% yield along with a mixture of byproducts that could not be identified by ^{1}H NMR analysis (entry 4). Interestingly, the analogous reaction with **2f** gave the deprotected amino-enyne adduct **3u**, albeit in a markedly lower yield of 15% along with recovery of **1a** in 55% yield (entry 5). In addition, reaction of **1a** with a more nucleophilic nitrogen source such as **2g** did not proceed as anticipated. Under our experimental conditions, the reaction afforded amino-substituted adduct **6a** as the sole product in 62% yield (entry 6).

(10) Fraxedas, J. *Molecular Organic Materials: From Molecules to Crystalline Solids*; Cambridge University Press: Cambridge, 2006. (b) Kleeman, A.; Engel, J. *Pharmaceutical Sustances: Synthesis, Patents, Applications*, 4th ed.; Thieme: Stuttgart, 2001. (c) Humphrey, M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243.

(11) Similar to that found in optimization studies with **1a** and **2a**, trace amounts of the dimers **4** and **5** were also detected in the ^{1}H NMR spectra of the crude mixtures of the enyne products shown in Table 2. However, these side products were not spectroscopically characterized due to the very small quantities obtained after flash column chromatography.

TABLE 2. Yb(OTf)$_3$-Catalyzed Amination of 1b−p with 2a[a]

entry	alcohol	time (h)	product	yield (%)
1	**1b**, R^1 = H, R^2 = F	2	**3b**, R^1 = H, R^2 = F	70
2	**1c**, R^1 = H, R^2 = Cl	2	**3c**, R^1 = H, R^2 = Cl	67
3	**1d**, R^1 = H, R^2 = Br	4	**3d**, R^1 = H, R^2 = Br	68
4	**1e**, R^1 = Me, R^2 = OMe	12	**3e**, R^1 = Me, R^2 = OMe	56
5	**1f**	7	**3f**	70
6	**1g**	12	**3g**, R = H	30
7	**1h**	5	**3h**, R = Bn	55
8	**1i**	10	**3i**	40
9	**1j**, R = OMe, n = 3	2	**3j**, R = OMe, n = 3	59
10	**1k**, R = H, n = 5	3	**3k**, R = H, n = 5	73
11	**1l**	5	**3l**	72[b]
12	**1m**	3	**3m**	67
13	**1n**	4	**3n**	67
14	**1o**	2	**3o**	61
15	**1p**	24	**3p**	-[c]

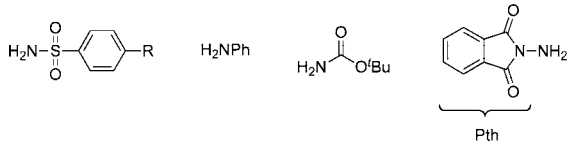
[a] All reactions were performed at 100 °C with Yb(OTf)$_3$/**1/2a** ratio of 1:20:40. [b] Isolated as a mixture of *Z*/*E* isomers in a ratio of 83:17. [c] No reaction based on TLC and ^{1}H NMR analysis of the crude mixture.

We tentatively propose the present Yb(OTf)$_3$-catalyzed conjugated enyne forming reaction to proceed by the mechanism outlined in Scheme 2, although it is highly speculative. This could involve activation of the alcohol substrate through coordination with the hydroxyl functionality. This delivers an ytterbium(III)-chelated intermediate **7** which can undergo elimination to give a putative carbocation species **8** and [Yb]-OH, which releases the metal catalyst by protodemetalation. It is possible that this newly formed cationic species subsequently undergoes cyclopropylcarbinol homoallylic rearrangement and trapping with **2** to deliver the enyne **3**.[12] The obtained *E*/*Z* product stereoselectivities could be due to the carbocation intermediate **8** adopting the conformer shown in Scheme 2 that would limit unfavorable steric interactions between the substituents and cyclopropane ring protons.[13] The role of the catalyst in facilitating dehydroxylation of the alcohol substrate would account for our earlier findings showing no product formation for the reaction of **1p** with **2a** (entry 15 in Table 2). It would not be inconceivable that such interactions are presumably weakened due the introduction of a strongly chelating pyridine moiety on the alcohol substrate. The origin of the *N*,*N*-aminophthalimide product **6a** could be due to direct attack of this resultant carbocation species by **2g** before ring fragmentation could occur. Indeed, this is further supported by the fact that, when a toluene solution containing **1a** was treated with indole **9** under the conditions shown in Scheme 3, the indole-substituted adduct **6b** was obtained in 99% yield. In these reactions, the exclusive formation of **6a** and **6b** suggested that, when a carbocation species such as **8** cannot be regenerated, the cyclopropane moiety is resistant to the ring opening process.

(12) A similar mechanism involving in situ formation of a cyclopropylmethyl carbocation has also been proposed for catalytic hydroamination of methylenecyclopropanes, see: (a) Siriwardana, A. I.; Kathriarachchi, K. K. A. D. S.; Nakamura, I.; Yamamoto, Y. *Heterocycles* **2005**, *66*, 333. (b) Chen, Y.; Shi, M. *J. Org. Chem.* **2004**, *69*, 426. (c) Shi, M.; Chen, Y.; Xu, B.; Tang, J. *Tetrahedron Lett.* **2002**, *43*, 8019.

(13) For similar *E*/*Z* stereoselectivties observed in other cyclopropylmethyl carbocation fragmentation processes, see: Honda, M.; Mita, T.; Nishizawa, T.; Sano, T.; Segi, M.; Nakajima, T. *Tetrahedron Lett.* **2006**, *47*, 5751, and references therein. .

TABLE 3. Yb(OTf)$_3$-Catalyzed Amination of 1a with 2b−g[a]



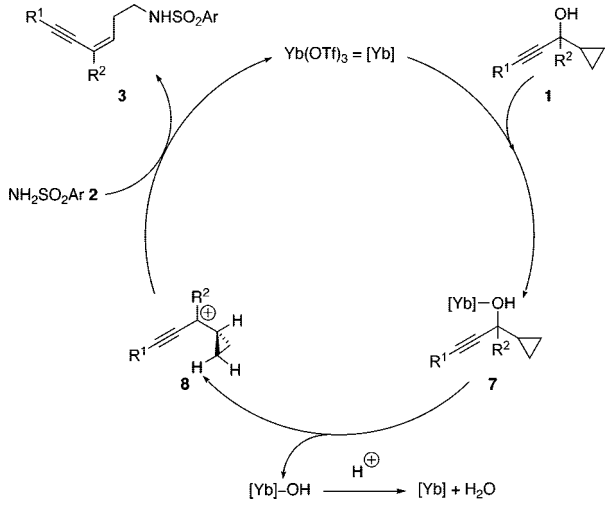
2b, R = H
2c, R = OMe
2d, R = Cl

2e **2f** **2g**

entry	nucleophile	time (h)	product	yield (%)
1	**2b**	5	**3q**, R = H	60
2	**2c**	1	**3r**, R = MeO	80
3	**2d**	2	**3s**, R = Cl	69
4	**2e**	12	**3t**	31
5	**2f**	24	**3u**	15[b]
6	**2g**	6	**6a**	62

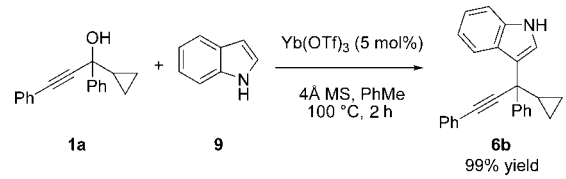
[a] All reactions were performed at 100 °C with Yb(OTf)$_3$/**1a**/**2** ratio of 1:20:40. [b] Starting alcohol **1a** recovered in 55% yield.

SCHEME 2. Tentative Mechanism for Yb(OTf)$_3$-Catalyzed Amination of 1-Cyclopropylprop-2-yn-1-ols with Sulfonamides



In summary, an efficient ytterbium-catalyzed synthetic route to conjugated enynes based on nucleophilic ring opening of unactivated 1-cyclopropyl-2-propyn-1-ols with arylsulfonamides has been reported. These results show that the reaction tolerates a structurally diverse set of alcohol substrates and complement earlier works with terminal and activated starting alcohols mediated by Ru$_2$[3] and Au[5] catalysts. The product yields and regioselectivity obtained are also comparable. In addition, the present method benefits from the use of not only alcohol substrates that can be accessed in one step from commercially available and low cost starting materials but also an ytterbium catalyst that is also less expensive. Our studies suggest Yb(OTf)$_3$-mediated activation of the substituted 1-cyclopropyl-2-propyn-1-ol substrate that leads to ionization of the alcohol. This possibly triggers subsequent ring opening of the cyclopropane moiety followed by trapping with the sulfonamide nucleophile to give the conjugated enyne product. Efforts to apply the method to natural product synthesis are currently underway and will be reported in due course.

SCHEME 3. Yb(OTf)$_3$-Catalyzed Reaction of 1a with Indole 9



1a **9** **6b**
99% yield

Experimental Section

Representative Experimental Procedure for Yb(OTf)$_3$-Catalyzed Preparation of Conjugated Enyne 3: To a solution of **1a** (74.5 mg, 0.3 mmol), **2a** (102.7 mg 0.6 mmol), and 4 Å molecular sieves (200 mg) in toluene (3 mL) was added Yb(OTf)$_3$ (9.3 mg, 15 μmol) under an argon atmosphere. The reaction mixture was stirred at 100 °C and monitored to completion by TLC analysis. The crude mixture was filtered through Celite, washed with EtOAc (20 mL), and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 7:1) furnished **3a** (90 mg, 75%) as a pale yellow oil.

Acknowledgment. This work is supported by a University Research Committee Grant (RG55/06) and Supplementary Equipment Purchase Grant (RG134/06) from Nanyang Technological University. The authors would like to thank the reviewers for their comments and suggestions.

Supporting Information Available: Characterization data and ^{1}H and ^{13}C NMR spectra for the starting alcohols **1** and conjugated enyne products **3**, NOE spectra of compounds **3e**, **3g**, and **3m**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8024626