# Intramolecular [2 + 2] Cycloaddition Reactions of Alkynyl Ether Derived Ketenes. A Convenient Synthesis of Donor−Acceptor Cyclobutanes
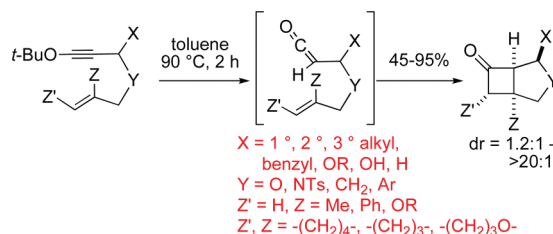
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## ABSTRACT



Mild thermolysis of *tert*-butyl alkynyl ethers furnishes aldoketenes, which undergo facile [2 + 2] cycloaddition reactions with pendant di- and trisubstituted alkenes. A wide variety of cis-fused cyclobutanones are produced in moderate to high diastereoselectivity and good to excellent yields by this method, and free hydroxyl groups are tolerated in the ene-ynol ether starting materials. Enol-ynol ethers also undergo efficient reaction to produce donor−acceptor cyclobutanes in high yields.

Cyclobutanones are useful starting materials for organic synthesis, since they are an excellent source of cyclopentanones (by one-carbon ring expansion), $\gamma$-butyrolactones (by peracid oxidation), and butyrolactams (by Beckmann rearrangement), moieties that form the core of numerous natural products.[1] The efficient preparation of substituted cyclobutanones is thus an important area of current synthetic methods research.

Cyclobutanones have been most frequently prepared by the cycloaddition of ketenes or ketiminium salts with olefins.[2] The intramolecular variant of this process, which gives rise to fused cyclobutanones, has been previously studied by the groups of Marko,[3] Snider,[4] and Brady.[5] The ketene intermediates utilized for the [2 + 2] cycloaddition are most frequently generated from the corresponding acid chlorides by treatment with $NEt_3$ at elevated temperatures. The use of moisture-sensitive and/or unstable acid chlorides may constitute a drawback of this method, as well as the necessity of employing triethylamine at high temperatures for base-sensitive substrates.

Ynol ethers possess significant potential in organic chemistry for the formation of carbon−carbon bonds.[6,7] The pioneering studies of Ficini[8] and Arens[9] have shown

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(2) (a) Lee-Ruff, E. In *The Chemistry of Cyclobutanes*; Rappoport, Z., Liebman, J. F., Eds.; J. Wiley & Sons: Chichester, NY, 2005; p 281. (b) Ghosez, L.; O'Donnell, M. J. *Pericyclic Reactions*; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. II, p 79. (c) Ghosez, L.; Marchand-Brynaert, J. *Iminium Salts in Organic Chemistry Part 1*; Bohme, J., Viehe, H. G., Eds.; Wiley: New York, 1976; p 421. (d) Falmagne, J. B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 879. (e) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793.

(3) Marko, I.; Ronsmans, B.; Hesbain-Frisque, A.-M.; Dumas, S.; Ghosez, L. *J. Am. Chem. Soc.* **1985**, *107*, 2192.

(4) (a) Snider, B. B.; Hui, R. A. H. F.; Kulkarni, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 2194. (b) Lee, S. Y.; Kulkarni, Y. S.; Burbaum, B. W.; Johnston, M. I.; Snider, B. B. *J. Org. Chem.* **1988**, *53*, 1848.
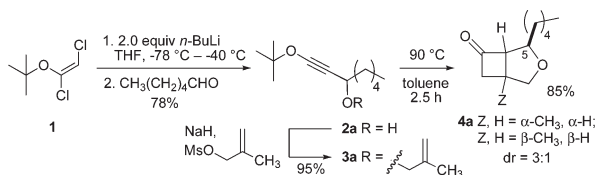
(5) Brady, W. T.; Giang, Y. F. *J. Org. Chem.* **1985**, *50*, 5177.

(6) For reviews of the chemistry of ynol ethers and the methods for the synthesis of ynol ethers, see: (a) Brandsma, L.; Bos, H. J.; Arens, J. F. In *The Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 751−860. (b) Stang, P. J.; Zhdankin, V. V. In *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; John Wiley & Sons: New York, 1994; Chapter 19.

that ethoxyacetylenes extrude ethylene gas at temperatures in excess of 100 °C, and the resulting ketenes undergo dimerization reactions or can be trapped by nucleophiles to form carboxylic acid derivatives. Significantly, *tert*-butyl alkynyl ethers undergo the retro-ene reaction with liberation of isobutylene gas at much lower temperatures (> 50 °C),[6a] and this process has been utilized recently by MaGee,[10] Magriotis,[11] Funk,[12] and Danheiser[13] for the preparation of lactones, lactams, amides, and cyclic imides. We were interested in exploring the utility of *tert*-butyl alkynyl ethers as ketene precursors for [2 + 2] cycloaddition reactions with alkenes, and in this Letter we report the successful application of this strategy to the synthesis of diverse cyclobutanones.

Following the protocol of Danheiser et al.,[13] treatment of 1,2-dichlorovinyl *tert*-butyl ether **1** (Scheme 1) with 2.0 equiv of *n*-BuLi in THF at −78 °C, followed by addition of hexanal and warming to room temperature, furnished alkynyl ether **2a** in 78% yield. Reaction of **2a** with methallyl mesylate in the presence of sodium hydride (THF, 0 °C→rt) then provided enyne test substrate **3a** in 95% yield. Heating a 0.01 M toluene solution of **3a** for 2 h at 90 °C under argon led to the production of cyclobutanone **4a** in 85% yield as a 3:1 mixture of diastereomers. It should be noted that attempting this process using the corresponding ethyl alkynyl ether (prepared from commercially available ethoxyacetylene), which required heating the substrate in excess of 120 °C to achieve starting material conversion, led to none of the desired cyclobutanones **4**, furnishing instead a complex mixture of UV-active products.

**Scheme 1.** Synthesis of Ene-Ynol Ether **3a** and Thermal Transformation to Cyclobutanone **4a**

To explore the scope of this process, substrates **3b**−**3g** (Table 1) were prepared in a similar fashion (see Supporting Information) and subjected to heating in toluene for 1−3 h. A variety of cyclobutanone-fused carbo- and heterocyclic ring systems were formed in good to excellent yields, and high diastereoselectivities were obtained for substrates bearing sterically demanding X-substituents (such as *i*-Pr and *t*-Bu, entries 3−5). Interestingly, the lowest diastereoselectivities (∼1:1) were observed for substrates possessing silyl ether groups at C.5 (entries 6 and 7). Crosspeaks observed in the NOESY spectrum of cyclobutanone **4b** (Figure 1 and Supporting Information) indicate that the major diastereomer formed in these reactions possesses the 2,3-*syn*, 2,5-*syn* stereochemistry, in accord with literature precedent for similar ketene-olefin cycloadditions.[14] The observed stereochemistry likely arises from a substrate conformer in which the C.5 substituent adopts a pseudoequatorial position in the transition state for [2 + 2] cycloaddition.

**Table 1.** Scope of the Thermal Retro-ene/[2 + 2] Cycloaddition Reaction of Ene-Ynol Ethers **3**[a]

| entry | X | Y | Z | 3 | % yield[b] 4 | d.r. |
|-------|---|---|---|---|---|------|
| 1 | CH$_3$(CH$_2$)$_4$ | O | CH$_3$ | a | 85 | 3:1 |
| 2 | CH$_2$Ph | O | CH$_3$ | b | 90 | 4:1 |
| 3 | (CH$_3$)$_2$CH | O | CH$_3$ | c | 78 | >95:5 |
| 4 | (CH$_3$)$_3$C | O | CH$_3$ | d | 64 | >95:5 |
| 5 | (CH$_3$)$_3$C | NTs | CH$_3$ | e | 92 | >95:5[c] |
| 6 | OTIPS | CH$_2$ | CH$_3$ | f | 60 | 1.2:1 |
| 7 | OTBDPS | CH$_2$ | Ph | g | 81 | 1.2:1 |

[a] Representative conditions for the transformation **3**→**4**: toluene (0.01 M), 2.5 h, 90 °C. [b] Isolated yield after chromatographic purification. [c] NOESY data for **4e** indicate that the major diastereomer possesses the 2,3-*syn*, 2,5-*anti* stereochemistry (see Supporting Information).
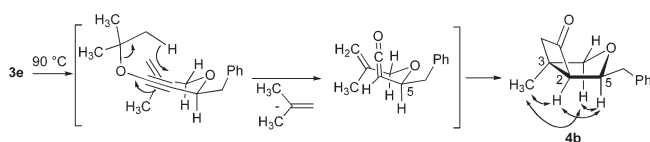
**Figure 1.** Proposed mechanistic model and stereochemical assignment of major diastereomer **4b** based on correlations observed in its NOESY spectrum.

During our studies we discovered that employing aromatic aldehydes for the generation of enyne substrates in the above protocol proved troublesome. While addition of *tert*-butoxyethynyllithium to benzaldehyde proceeded uneventfully, all attempts to install the methallyl ether moiety by base-promoted S$_N$2 reaction led to extensive substrate

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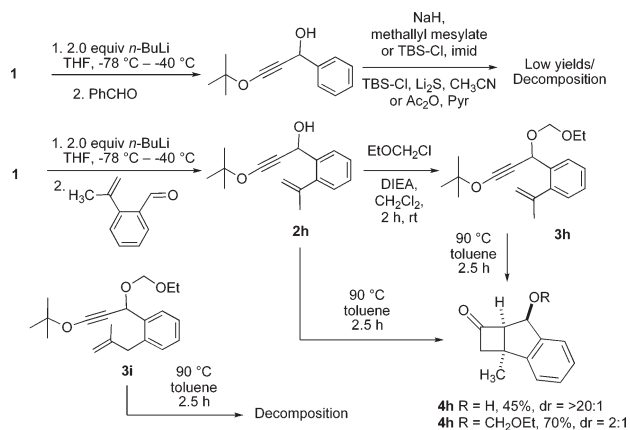(12) Funk, R. L.; Abelman, M. M.; Jellison, K. M. *Synlett* **1989**, 36.

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decomposition (Scheme 2). Furthermore, silylation (TBS-Cl, imid, DMF; TBS-Cl, Et$_3$N, DMAP; TBS-Cl, Li$_2$S,[16] CH$_3$CN) or acylation (Ac$_2$O, Pyr) of such benzylic propargylic alcohols under mildly basic conditions led only to low yields (<10%) of product; acid-catalyzed processes (DHP, cat. PPTS) afforded α,β-unsaturated esters arising from the well-known Meyer–Schuster rearrangement.[15] Ultimately it was found that enyne alcohol **2h** could be protected as its ethoxymethyl acetal in high yield by treatment with chloromethyl ethyl ether and excess DIEA in CH$_2$Cl$_2$ at room temperature for 2 h. The obtained acetal (**3h**) was a suitable substrate for the retro-ene/cycloaddition reaction, giving rise to cyclobutanone **4h** (R = CH$_2$OEt) in 70% yield and 2:1 diastereoselectivity upon heating at 90 °C in toluene for 2 h. Interestingly, it was also found that heating unprotected benzylic alcohol **2h** under our standard conditions gave rise to cyclobutanone **4h** (R = H) in 45% yield *but with > 20:1 diastereoselectivity*. The dramatically increased stereoselectivity for this substrate relative to enynes bearing protected alcohols (**3h**, **3f**, and **3g**) is perhaps indicative of the existence of an interaction between the hydroxyl proton and the π-system of either the ketene or alkene in the transition state for [2 + 2] cycloaddition. The successful cyclization of a substrate bearing an unprotected alcohol represents an advantage of this method over other procedures for ketene generation involving acid chlorides, since clearly unprotected alcohols in such substrates would be highly prone to inter-/intramolecular esterification reactions under basic conditions. Efforts to improve the yield of cyclobutanone formation for enynes bearing unprotected alcohols are underway, as well as an analysis of the scope and origins of the high stereoselectivity of this process. In line with Marko's observation[3] that increasing the tether length between alkene and ketene suppresses cycloaddition, thermolysis of the homologous ene-ynol ether **3i**[17] under our standard conditions gave negligible amounts of cyclobutanone products.

To broaden the substrate scope of this process, alternative approaches to the enyne cyclization substrates were next investigated. The nucleophilic substitution reaction of appropriate alkyl halides with *tert*-butoxyethynyllithium in THF/HMPA[18] furnished enynes **3j** and **3m**. Reaction of **1** with *n*-BuLi, followed by treatment with excess paraformaldehyde, gives rise to 3-*tert*-butoxyprop-2-yn-1-ol, which was not purified but rather directly combined with appropriate allylic methanesulfonates under basic conditions to give rise to enynes **3k**–**l** and **3n**–**o** (Scheme 3).

As can be seen in Table 2, whereas enyne substrate **3j** bearing a floppy carbon tether between the alkynyl ether and alkene moieties gave negligible amounts of **4j** under standard reaction conditions (entry 1), substrates with tethers containing an oxygen atom (**3k**, **3l**, **3n**, **3o**, entries 2, 3, 5, 6) or unsaturated carbon atoms (**3m**, entry 4) gave good yields of cyclobutanone products. The use of trisub-

**Scheme 3.** Methods for the Preparation of Enynes **3j**–**3o**

**Scheme 2.** Employing Protected and Unprotected Benzylic Alcohols in the Cyclization Process

**Table 2.** Thermal Retro-ene/[2 + 2] Cycloaddition Reaction of Substrates **3j**–**3o**[a]

| entry | 3 | 4 | % yield[b] 4 |
|---|---|---|---|
| 1 | **3j** | **4j** | <5 |
| 2 | **3k** | **4k** | 50[c] |
| 3 | **3l** | **4l** | 69 |
| 4 | **3m** | **4m** | 55 |
| 5 | **3n** | **4n** | 65 |
| 6 | **3o** | **4o** | 61 |

[a] Representative conditions for the transformation **3**→**4**: toluene (0.01 M), 2.5 h, 90 °C. [b] Isolated yield after chromatographic purification. [c] The low isolated yields are due to the high volatility of cyclobutanone **4k**.

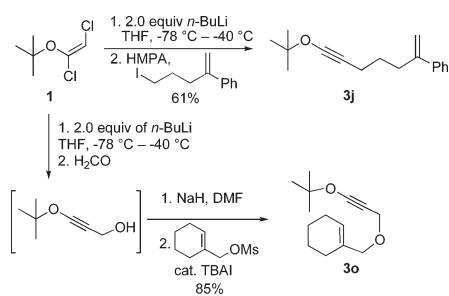(15) For a recent review of the Meyer–Schuster rearrangement, see: Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, 7, 4149.

**Table 3.** Thermal Retro-ene/[2 + 2] Cycloaddition Reaction of Ynol-Enol Ethers **3p–3t**

| entry | 3 | 4 | % yield[b] 4 | dr |
|-------|---|---|--------------|-----|
| 1 | **3p** | **4p** | 89 | 3:1 |
| 2 | **3q** | **4q** | 95 | 8:1 |
| 3 | **3r** | **4r** | 65 | >95:5 |
| 4 | **3s** | **4s** | 75 | — |
| 5 | **3t** | **4t** | 81 | 1.3:1 |



[a] Representative conditions for the transformation **3→4**: toluene (0.01 M), 2.5 h, 90 °C. [b] Isolated yield after chromatographic purification.

stituted alkenes is also well tolerated, allowing the preparation of fused tricyclic compounds **4n** and **4o**.

Finally, we wished to examine the feasibility of preparing donor–acceptor cyclobutanes utilizing this protocol. Substrate ynol-enol ethers **3p–3t** were prepared[19] by the above-mentioned protocols (see Supporting Information) and heated in toluene solution at 90 °C for 2 h to provide cyclobutanones **4p–4t** cleanly and in high yields (Table 3). In comparison to the methyl-substituted cyclobutanones **4b**, **4d**, and **4h**, slightly diminished diastereoselectivities were observed in the formation of cyclobutanones **4p**, **4q**,

and **4t**, which is likely due to the decreased steric requirements of the ether substituent in the transition state for [2 + 2] cycloaddition. Again, the NOESY spectrum of cycloadduct **4p** confirmed the 2,3-*syn*, 2,5-*syn* stereochemistry for these substrates. Although cyclobutanones **4p–t** proved to be quite sensitive to Bronsted and Lewis acids,[20] compound **4q** could be smoothly transformed into lactone **5q** in 92% yield by an MCPBA-mediated Baeyer–Villiger reaction (Scheme 4).

In summary, we have shown that ynol ether-alkenes and enol-ynol ethers produce the corresponding cyclobutanones under mild, neutral conditions in good to excellent yields and diastereoselectivities. Notably, substrates bearing unprotected hydroxyl groups are also tolerated in this protocol. Investigation of the Lewis acid promoted cycloaddition and ring expansion reactions of the donor–acceptor cyclobutanes available by this protocol is currently underway and will be reported in due course.

**Scheme 4.** Baeyer–Villiger Oxidation of **4q**

**Supporting Information Available.** Experimental details, characterization data, ^{1}H, ^{13}C spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.
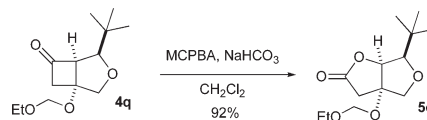
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(17) Compound **3i** was prepared in four steps from commercially available 2-bromobenzaldehyde diethyl acetal by copper-catalyzed allylation of the corresponding Grignard reagent (Mg, THF; cat. CuI, methallyl mesylate), hydrolysis of the diethyl acetal (acetone, cat. TsOH), addition of *tert*-butoxyethynyllithium (THF, −78 °C), and protection of the benzylic alcohol as its ethoxymethyl acetal (EtOCH₂Cl, DIEA, 2 h, rt). See: Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 12901.

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(20) Matsuo has demonstrated Lewis acid promoted formal [4 + 2] cycloaddition reactions between 3-alkoxycyclobutanones and aldehydes, ketones, allylsilanes, and silylenol ethers: (a) Matsuo, J.-i.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Org. Lett.* **2009**, *11*, 3822. (b) Matsuo, J.-i.; Negishi, S.; Ishibashi, H. *Tetrahedron. Lett.* **2009**, *50*, 5831. (c) Matsuo, J.-i.; Sasaki, S.; Tanaka, H.; Ishibashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 11600.