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Tandem Bond-Forming Reactions of 1-Alkynyl Ethers

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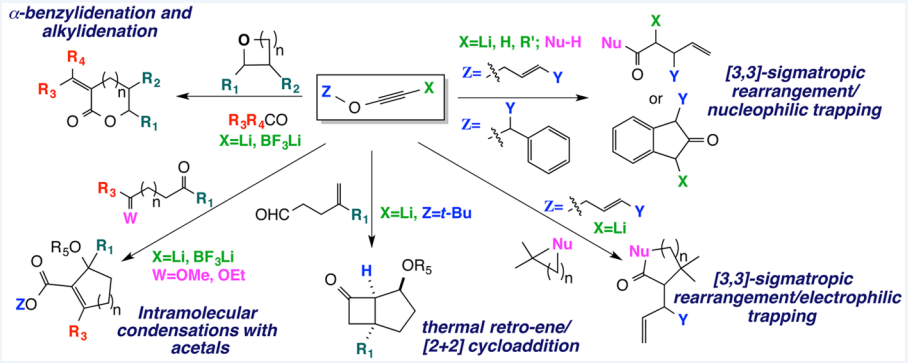

CONSPECTUS: Electron-rich alkynes, such as ynamines, ynamides, and ynol ethers, are functional groups that possess significant potential in organic chemistry for the formation of carbon−carbon bonds. While the synthetic utility of ynamides has recently been expanded considerably, 1-alkynyl ethers, which possess many of the reactivity features of ynamides, have traditionally been far less investigated because of concerns about their stability. Like ynamides, ynol ethers are relatively unhindered to approach by functional groups present in the same or different molecules because of their linear geometry, and they can potentially form up to four new bonds in a single transformation. Ynol ethers also possess unique reactivity features that make them complementary to ynamides.

Research over the past decade has shown that ynol ethers formed in situ from stable precursors engage in a variety of useful carbon−carbon bond-forming processes. Upon formation at −78 °C, allyl alkynyl ethers undergo a rapid [3,3]-sigmatropic rearrangement to form allyl ketene intermediates, which may be trapped with alcohol or amine nucleophiles to form γ,δ-unsaturated carboxylic acid derivatives. The process is stereospecific, takes place in minutes at cryogenic temperatures, and affords products containing (quaternary) stereogenic carbon atoms. Trapping of the intermediate allyl ketene with carbonyl compounds, epoxides, or oxetanes instead leads to complex α-functionalized β-, γ-, or δ-lactones, respectively. [3,3]-Sigmatropic rearrangement of benzyl alkynyl ethers also takes place at temperatures ranging from −78 to 60 °C to afford substituted 2-indanones via intramolecular carbocyclization of the ketene intermediate.

tert-Butyl alkynyl ethers containing pendant di- and trisubstituted alkenes and enol ethers are stable to chromatographic isolation and undergo a retro-ene/[2 + 2] cycloaddition reaction upon mild thermolysis (90 °C) to afford cis-fused cyclobutanones and donor−acceptor cyclobutanones in good to excellent yields and diastereoselectivities. This process, which takes place under neutral conditions and proceeds through an aldoketene intermediate, obviates the need to employ moisture-sensitive and/or unstable acid chlorides under basic conditions for intramolecular [2 + 2] cycloaddition reactions. Furthermore, Lewis acid-catalyzed intramolecular condensations of both ethyl and *tert*-butyl ynol ethers with tethered acetals efficiently provide protected five-, six-, and seven-membered cyclic Baylis−Hilman adducts. Metalated ethoxyacetylene can also participate in multiple bond-forming reactions that avoid isolation of the alkynyl ether intermediate. Lewis acid-promoted tandem additions employing epoxides/oxetanes and carbonyl compounds give rise to (*Z*)-α-alkylidene and α-benzylidene lactones stereoselectively in high overall yields. Three new carbon−carbon bonds and a ring are formed in this atom-economical single-flask transformation, resulting in a significant increase in molecular complexity.

This Account provides a detailed overview of these useful transformations with the intention of stimulating further interest in and research on ynol ethers and their application in organic synthesis.

1. INTRODUCTION

The ynol ether functional group possesses a highly polarized triple bond, giving it heightened reactivity as both an electrophile (at C1) and as a nucleophile (at C2) (Figure 1).[1] For example, it can be envisioned that sequential reactions of ynol ether **A** with an electrophile (El) and then a nucleophile (Nu) would give rise to enol ether **B**, which can rearrange to **C** or further react at C2 with an electrophile (El′) and at C1 with a nucleophile (Nu′) to provide a complex substituted ether such as compound **D** or α-substituted carbonyl compound **E**. Thus, up to four new covalent bonds may be fashioned in this process, and the tethering of

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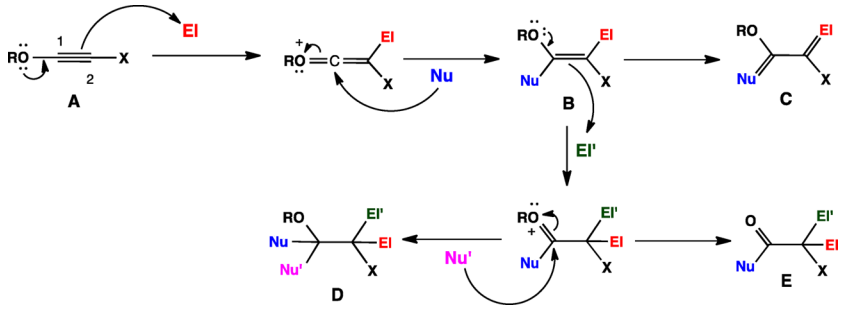


Figure 1. Reactivity of 1-alkynyl ethers.

an electrophile−nucleophile pair would allow a carbocyclic or heterocyclic ring to be formed. Historically, synthetic chemists have not taken full advantage of this potential reactivity pattern of ynol ethers, especially with respect to carbon−carbon bond formation. Only recently has the utility of silyl ynol ethers in [2 + 2] cycloadditions[37a] and ring-expansion processes[33] begun to be explored. Furthermore, while 1-alkynyl ethers have been commonly employed in (macro)lactone and lactam formation,[2] transition-metal-catalyzed processes,[3] and benzannulation reactions,[37b] concerns about the stability of ynol ethers have directed the attention of the synthetic community toward the ynamide functional group[4] and ynolates.[5]

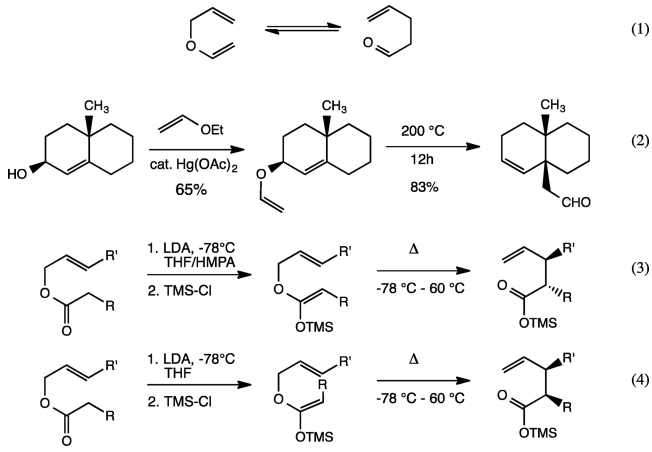
Over the past decade we have focused our attention on both the synthesis and reactivity of 1-alkynyl ethers and have discovered that this functional group indeed possesses important reactivity patterns that complement those available to ynamides. In this Account, we discuss our work on tandem bond-forming reactions of ynol ethers and highlight their utility in organic synthesis for the rapid buildup of molecular complexity.

2. [3,3]-SIGMATROPIC REARRANGEMENT OF ALLYL ALKYNYL ETHERS

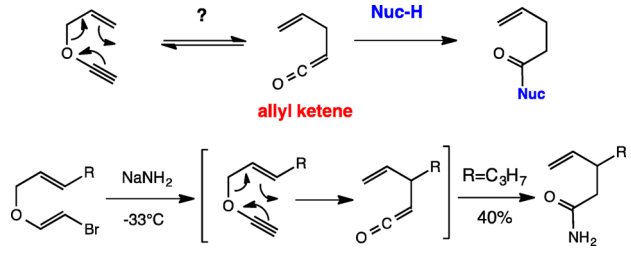
The [3,3]-sigmatropic rearrangement of allyl vinyl ethers (the Claisen rearrangement) is a powerful method for the formation of carbon−carbon bonds.[6] In this process, a C−O σ bond is broken and a C−C σ bond is formed in a highly stereospecific fashion; the concomitant exchange of a weaker alkene (C═C) bond for a stronger carbonyl (C═O) bond provides the thermodynamic driving force for the overall process. Uncatalyzed Claisen rearrangements take place under thermal conditions with temperatures typically in excess of 150 °C,[7] with measured activation barriers in the range of 28−32 kcal/mol.[8] The Ireland−Claisen rearrangement of allylic esters via their enolate or silyl enol ether forms is a particularly useful variant of the classic reaction that occurs at significantly lower temperatures (−78 to 60 °C) and with predictable and high diastereoselectivities based on control of the intermediate enol/enolate geometry (Scheme 1).[9]

We initially were interested in investigating whether allyl 1-alkynyl ethers would similarly participate in a Claisen-like [3,3]-sigmatropic process (Scheme 2). Once again, the exchange of a weaker C═C bond for a stronger C═O bond would provide the thermodynamic driving force for the rearrangement, with an allyl ketene being formed as the initial product. The allyl ketene could be trapped by reaction with an added nucleophile, giving rise to a γ,δ-unsaturated carbonyl compound. Although the early investigations of Arens[10] and Schmid[11] on the sigmatropy of benzyl alkynyl ethers (vide infra) along these lines were encouraging, evidence of the feasibility of this specific reaction manifold came from the work of Katzenellebogen,[12]

Scheme 1. Claisen Rearrangement (1): Thermal[7] (2) and Ireland−Claisen[9] (3, 4) Variants



Scheme 2. Allyl Alkynyl Ether Sigmatropy; Katzenellenbogen's Study[12]



who showed that treatment of allyl bromovinyl ethers with sodamide in refluxing ammonia produced pent-4-enamides in good yields. The proposed mechanism involved base-mediated dehydrohalogenation to form the allyl alkynyl ether followed by [3,3]-sigmatropic rearrangement and ketene trapping with amide ion. Although the remarkable facility of this rearrangement at low temperature was noted, at the time no further efforts were made to study this process.

The synthesis of 1-alkynyl ethers presented one of the first obstacles to studying the rearrangement reaction. As noted by Katzenellenbogen,[12] all attempts to prepare allyl alkynyl ethers directly by reaction of metal allyloxides with haloacetylenes fail, giving only acetylene dimers. In 1987, Greene[13] showed that 1,2-dichlorovinyl ethers could be transformed into lithioalkynyl ethers by treatment with 2 equiv of *n*-BuLi; protonation with methanol furnished terminal alkynyl ethers, while alkylation with iodoalkanes gave rise to substituted alkoxyacetylenes.[14] In 2000, Bruckner showed that a similar treatment of 1,1-dichlorovinyl ethers also provides ynol ethers.[15] Thus, we

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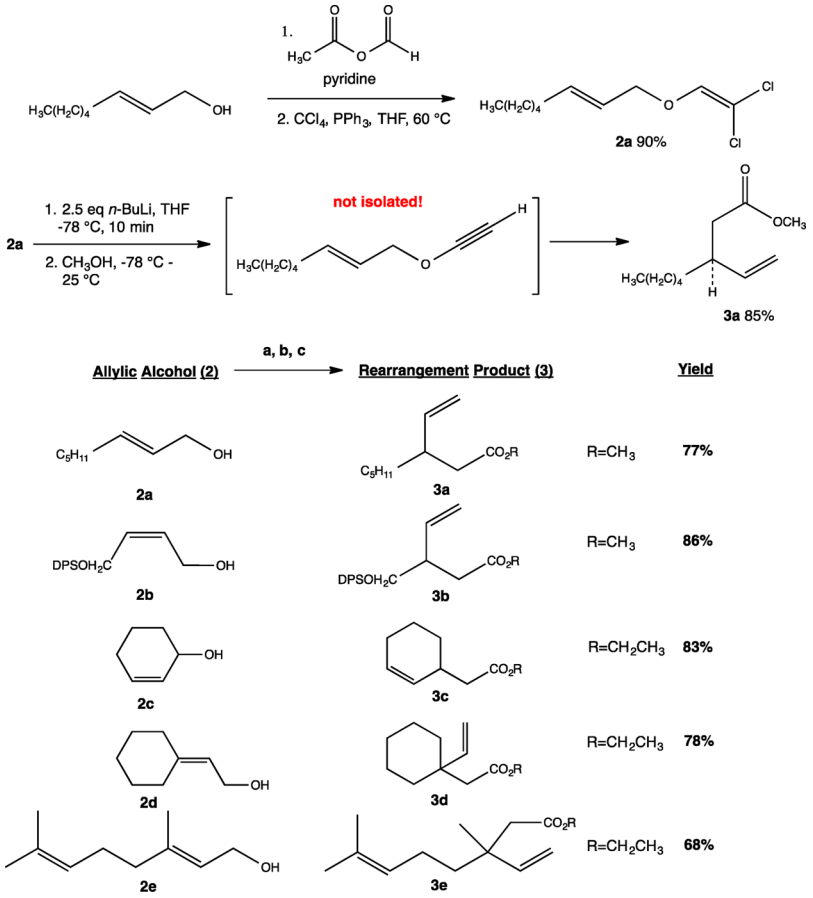
Scheme 3. Preparation and *n*-BuLi-Induced Rearrangement of Allyl 1,1-Dichlorovinyl Ethers



began our investigations by attempting to prepare dichlorovinyl ethers from allylic alcohols.

Greene's protocol for the synthesis of 1,2-dichlorovinyl ethers, involving reaction of metal alkoxides with trichloroethylene, proved unsatisfactory when applied to allylic alcohols, with the desired vinyl ethers being formed in <10% yield. However, Bruckner's two-step protocol involving alcohol formylation (with acetic formic anhydride and pyridine) and dichlorovinylation (PPh_3 and CCl_4) gave high yields of allyl 1,1-dichlorovinyl ethers (**2**) from a diverse array of allylic alcohols (Scheme 3). Treatment of vinyl ethers **2** with 2.2−2.5 equiv of *n*-BuLi (−78 °C, 10 min) followed by quenching of the reaction with excess ethanol or methanol gave rise not to the expected terminal alkynyl ethers but rather to the rearranged homoallylic esters in 68−86% overall yields. Remarkably, when 1,1-dichlorovinyl ethers of trisubstituted and cyclic allylic alcohols are employed in this reaction, products containing quaternary centers are formed efficiently within minutes at cryogenic temperatures.[16] Phenols, primary and secondary alcohols, amines, and oxazolidinones may be used as quenching agents to furnish γ,δ-unsaturated esters, amides, and imides.[17]

The stereospecificity of the rearrangement was probed with *cis*- and *trans*-carvyl 1,1- dichlorovinyl ethers **5a** and **5b**. Upon treatment with *n*-BuLi followed by ethanol quench, **5a** rearranged to *cis*-ethyl ester **6a** exclusively, whereas **5b** gave the *trans*-ethyl ester **6b** exclusively (Scheme 4). These results indicated that the rearrangement is indeed highly stereospecific, with carbon−carbon bond formation occurring on the same face of the molecule as carbon−oxygen bond cleavage. The requirement for a cyclic transition state was investigated with glucal-3-*O*-dichlorovinyl ethers **7** and **9**. Dibenzyl glucal derivative **7** rearranges smoothly to β-C-glycoside **8** in 65% yield upon exposure to *n*-BuLi at −78 °C followed by ethanol quench. However, conformationally restricted glucal-4,6-acetonide **9** gave none of the rearranged ester when subjected to the same conditions, producing only decomposition products when the reaction mixture was warmed to room temperature. Since the dichlorovinyl ether unit of **9** cannot access the axial conformation necessary to achieve close proximity of the reacting termini at C1 and C6′, these results provide evidence for the existence of a pathway involving a cyclic transition state.

Our initially proposed mechanism for this transformation involved base-mediated formation of a lithioalkynyl ether followed by sigmatropic rearrangement and reaction of the allyl ketene intermediate with the quenching agent. One critical observation provided insight into the early stages of the reaction: treatment of allyl 1,1-dibromovinyl ethers with *n*-BuLi at −78 °C followed by methanol quench gave a <10% yield of the expected rearranged products, furnishing instead a cis/trans mixture of monodebrominated products (Scheme 5). This result indicated that lithium−halogen exchange was likely not the first step of the mechanism but rather that vinyl ether deprotonation/chloride ion elimination occurred to provide a chloroalkynyl ether species;[18] subsequent rapid lithium−chloride exchange would then provide the lithioalkynyl ether. [3,3]-Sigmatropic rearrangement may then proceed either via the lithium acetylide (**15a**) to produce a lithioketene[39] (**16a**) or via protonated acetylene (**15b**, formed after addition of the alcohol quenching agent) to produce allyl ketene **16b**. Reaction of the lithioketene or allyl ketene with alcohol would then provide the observed

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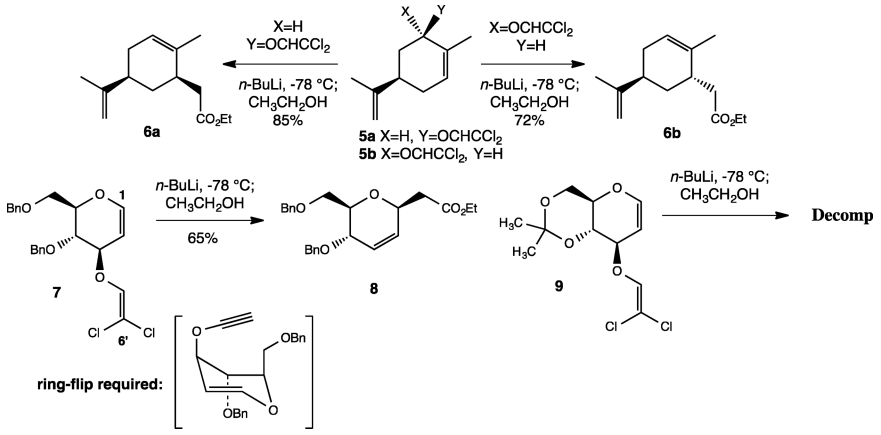
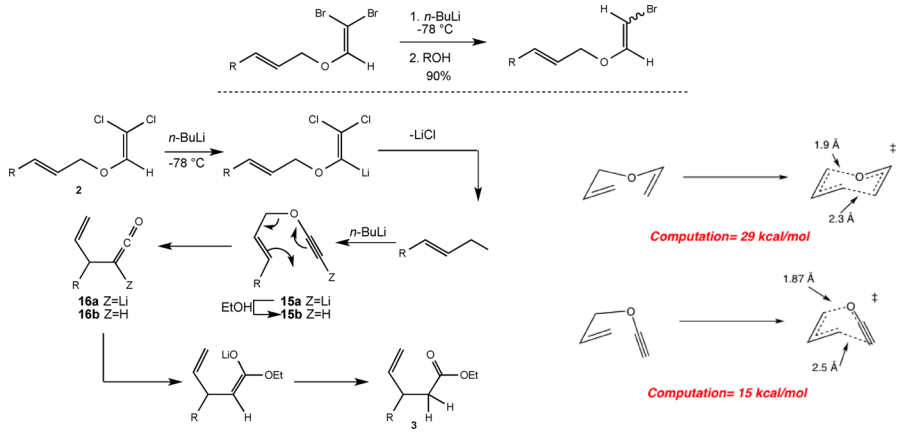
Scheme 4. Probing the Stereospecificity of the [3,3]-Sigmatropic Rearrangement



Scheme 5. Proposed Mechanism for the *n*-BuLi-Induced Rearrangement of Ethers 2



unsaturated ester product. An alternative means for preparing neutral allyl alkynyl ethers was subsequently developed (vide infra), and it was shown that these compounds undergo [3,3]-sigmatropic rearrangement at −78 °C, indicating the feasibility of the **15b** → **16b** pathway.[17] DFT calculations (B3LYP functional/6-21G9(d) basis set)[19] for the rearrangement of allyl ethynyl ether revealed an activation barrier of 15 kcal/mol, compared with a value of 29 kcal/mol computed for the Claisen rearrangement of allyl vinyl ether. Furthermore, an earlier transition state is apparent for allyl alkynyl ether sigmatropy, with less C−O bond cleavage and less advanced C−C bond formation compared with its allyl vinyl ether counterpart.

The mechanistic hypothesis forwarded indicates that a nucleophilic lithioalkynyl ether or lithioketene species is present in the reaction mixture prior to alcohol addition; an added electrophile should then be incorporated at the ester α-position. Indeed, treatment of vinyl ether **2c** with *n*-BuLi at −78 °C followed by methyl triflate or TMSCl (2 equiv) and then excess ethanol gave rise to α-substituted unsaturated esters in good yields, albeit with poor diastereoselectivity (Scheme 6). It was subsequently discovered that addition of symmetrical or unsymmetrical ketones to the anionic rearrangement mixture at −78 °C, followed by quench with saturated aqueous bicarbonate solution instead of alcohols, gave rise to β-lactones (**20**) in high overall yields.[20] Interestingly, the use of aldehydes in this reaction instead gave only low yields of the corresponding β-hydroxy acids. These results indicate the importance of the newly formed quaternary center for efficient cyclization of the presumed β-hydroxy ketene intermediate at low temperatures. Reaction of the anionic rearrangement intermediate with terminal and internal epoxides or substituted oxetanes in the presence of $BF_3{\cdot}OEt_2$ gave rise to complex γ- and δ-lactones, respectively, in very good overall yields. Thus, the electrophile-quenching manifold significantly extends the utility of allyl alkynyl ether sigmatropy, allowing highly substituted cyclic products to be prepared in a single-flask process from allyl 1,1-dichlorovinyl ethers.

A limitation of the above-described processes is the need for the strong nucleophilic base *n*-BuLi in the generation of the alkynyl ether species, a factor that may potentially limit the scope of the rearrangement reaction. In an attempt to develop milder conditions for preparing alkynyl ethers,[38] we reasoned that elimination reactions of enol triflates derived from α-alkoxy ketones might be performed with weaker, non-nucleophilic bases. Following the procedure of Muthusamy et al.,[21] α-alkoxy ketones were prepared in a single step from α-diazo ketones and alcohols in the presence of catalytic quantities of indium triflate (Scheme 7). The corresponding enol triflates, prepared as *Z* isomers exclusively by deprotonation (LiHMDS, THF, −78 °C) and triflation ($PhNTf_2$, DMPU, −78 °C to rt), were then treated with potassium *tert*-butoxide in THF at −78 °C. We were pleased to find that enol triflates derived from aryl, alkenyl, and alkynyl ketones all underwent facile elimination of triflate ion at low temperature to form the corresponding alkynyl ethers (**21**) in good yields.[17] Aliphatic α-alkoxy ketones, however, failed to produce isolable enol triflates upon exposure to LiHMDS/$PhNTf_2$.

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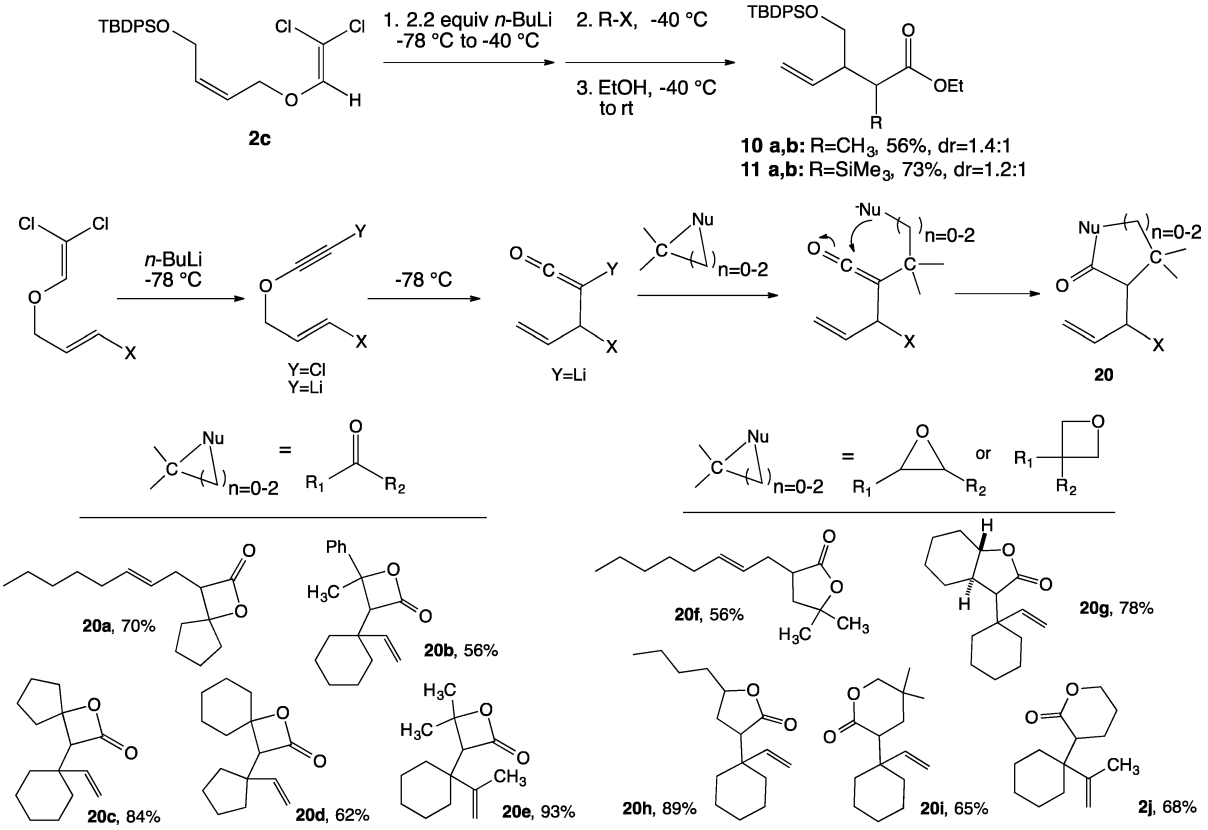
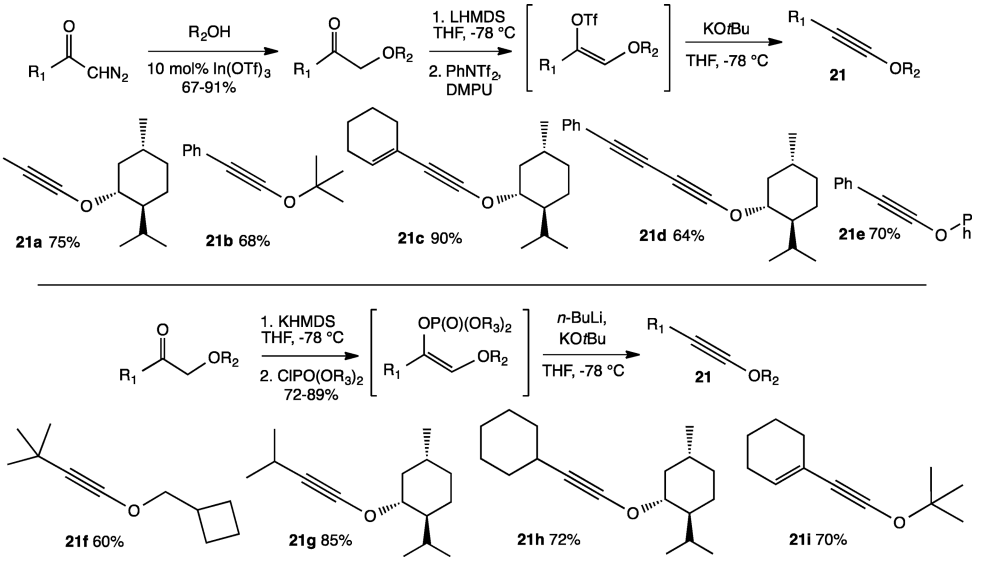
Scheme 6. Electrophile Trapping of the Anionic Rearrangement Intermediate



Scheme 7. Preparation of 1-Alkynyl Ethers from α-Alkoxy Ketones



It is likely that under the basic reaction conditions these enol triflates decompose in situ to form allenic compounds that undergo side reactions. Nonetheless, alkynyl ethers could be prepared from aliphatic α-alkoxy ketones by conversion first to the corresponding (*Z*)-enol phosphates (KHMDS, $ClPO(OR_3)_2$, THF, −78 °C) and subsequent elimination with Schlosser's base (*n*-BuLi, KO*t*-Bu, THF, −78 °C).

With an alternative method for preparing alkynyl ethers in hand, we wished to explore whether the [3,3]-sigmatropic rearrangement of neutral allyl alkynyl ethers prepared in situ would take place with equal facility. Indeed, exposure of enol triflate **23a**, derived in two steps from α-diazoacetophenone and prenyl alcohol, to excess KO*t*-Bu in THF at −78 °C and warming to room temperature gave rise to *tert*-butyl ester **24a**; performing the same reaction instead in the presence of 3 equiv of morpholine at −78 °C gave rise to amide **24b** (Scheme 8). Interestingly, while the reaction of enol triflate **23b** with potassium menthyloxide at −78 °C in THF gave rise to a 55% yield of the expected rearranged menthyl ester **24c**, the analogous reaction of **23b** with potassium methoxide furnished only α-alkoxy ketone

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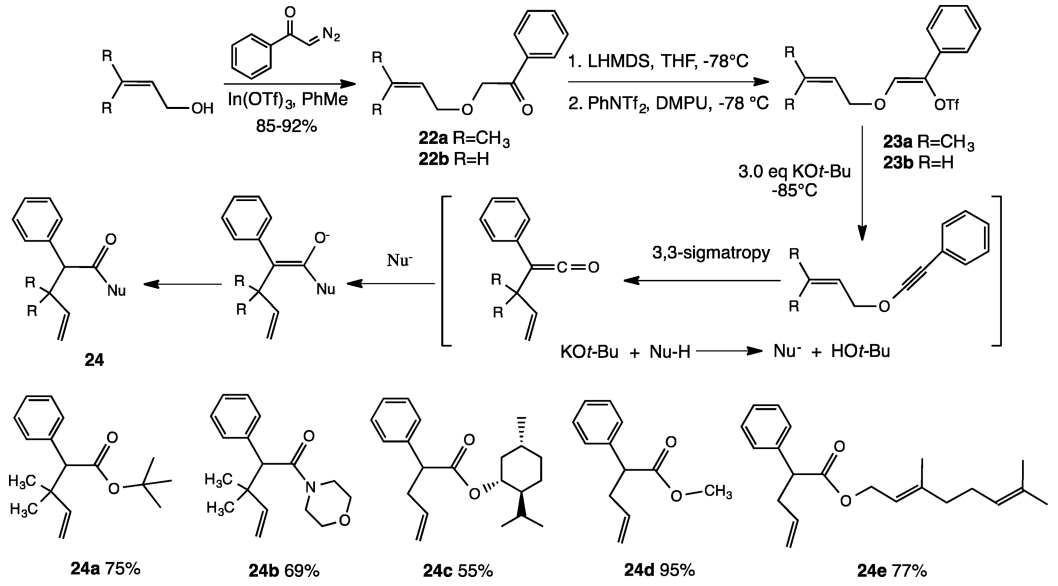
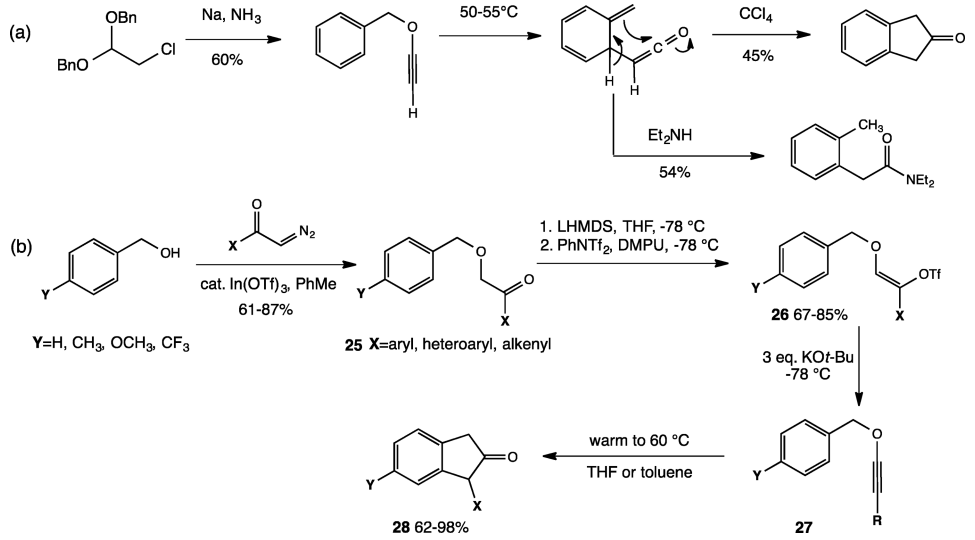
Scheme 8. [3,3]-Sigmatropic Rearrangement via KO*t*-Bu-Induced Elimination of Enol Triflates



Scheme 9. (a) Previous and (b) Current Examples of Benzyl Alkynyl Ether Sigmatropy



22b resulting from nucleophilic attack of methoxide at sulfur. However, it was found that rapid sequential addition of KO*t*-Bu (2.5 equiv) and methanol (2.5 equiv) to **22b** in THF at −85 °C furnished a 95% yield of the expected methyl ester **24d**. Repetition of this protocol with geraniol instead of methanol gave geranyl ester **24e** in 77% yield. These results imply that while deprotonation/elimination of the enol triflate by KO*t*-Bu is rapid at −85 °C, addition of KO*t*-Bu to the ketene intermediate is slow at this temperature (in contrast, elimination, sigmatropic rearrangement, and addition of KO*t*-Bu to the ketene intermediate at −78 °C are fast). Thus, the KO*t*-Bu remaining after triflate elimination rapidly deprotonates the added alcohol to form its alkoxide, which adds instead to the ketene to form **24d/e** upon protonation.

Having explored the [3,3]-sigmatropic rearrangement of allyl alkynyl ethers, we next decided to look at the analogous process for benzyl alkynyl ethers. Since the use of *n*-BuLi for the generation of benzyl alkynyl ethers from the corresponding dichlorovinyl ethers was precluded because of facile deprotonation of the benzylic carbon atom under strongly basic conditions, we again focused on the KO*t*-Bu-mediated elimination reaction of enol triflates as a method for the preparation of benzyl alkynyl ethers.

3. [3,3]-SIGMATROPIC REARRANGEMENT OF BENZYL ALKYNYL ETHERS

The first examples of benzyl alkynyl ether sigmatropy were seen in the work of Arens[10] and Schmid.[11] Sodamide-induced elimination reactions of α-chlorodibenzyl acetals furnished isolable benzyl alkynyl ethers, which produced 2-indanones upon heating in carbon tetrachloride or *o*-tolyl acetamides upon heating in the presence of amines. A [3,3]-sigmatropic process was proposed, providing a nonaromatic allyl ketene intermediate that was either trapped with nucleophiles or underwent ring closure to furnish the observed products (Scheme 9a).

We observed that α-alkoxy ketones are also viable precursors of benzyl alkynyl ethers: treatment of a variety of aryl-, heteroaryl-, and alkenyl α-benzyloxy ketones with LiHMDS and $NPhTf_2$ provided the corresponding enol triflates (**26**),

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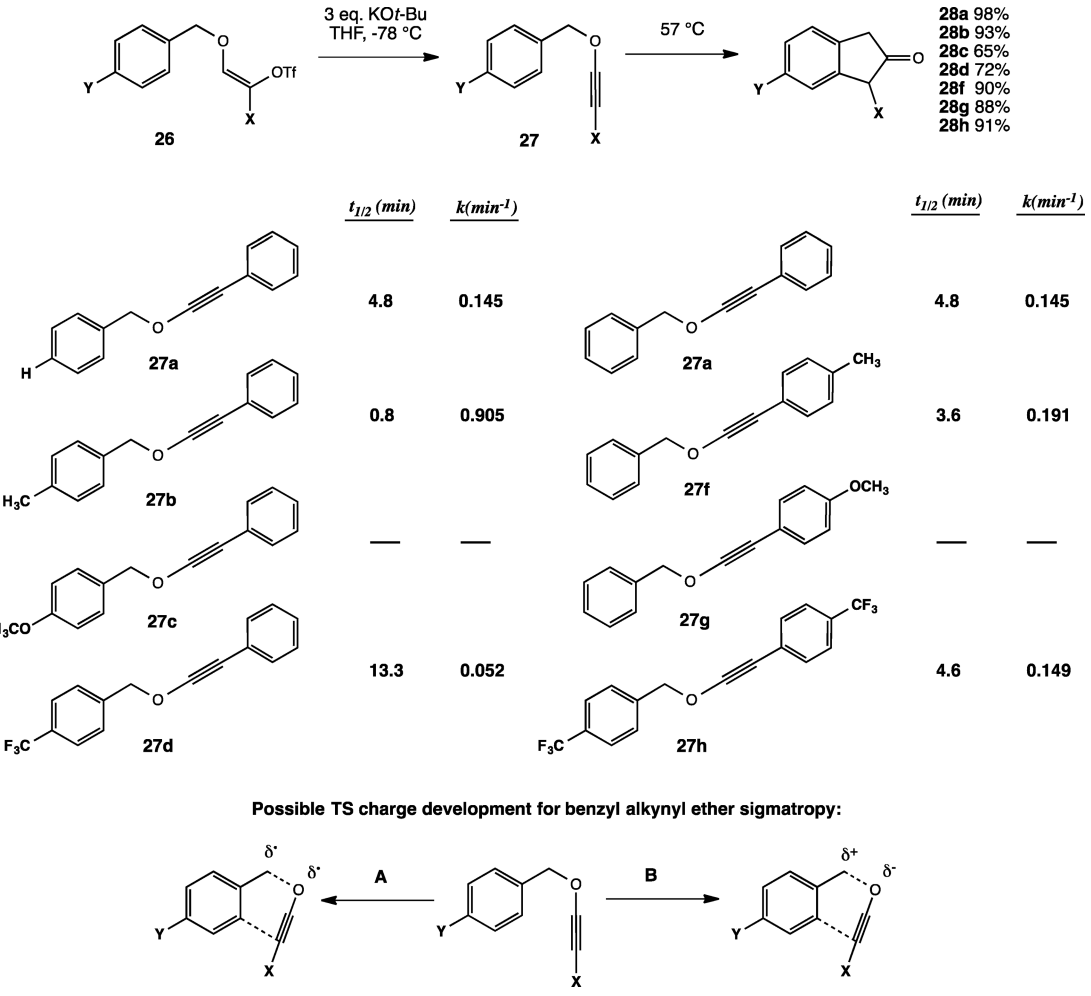
Scheme 10. Kinetic Data for Rearrangement of Substituted Benzyl Alkynyl Ethers



which underwent smooth elimination with KO*t*-Bu in THF at −78 °C to provide benzyl alkynyl ethers **27** (Scheme 9b).[22] Simply heating these ethers in toluene at 60 °C for 1 h induced rearrangement to 2-indanones **28** in high yields.

Studying the rates of rearrangement of substituted alkynyl ether substrates **27a−d** revealed some interesting trends (Scheme 10). Electron-donating groups on the benzyl moiety accelerate the rearrangement process: whereas the unsubstituted benzyl ether **27a** rearranged with a half-life of 4.8 min at 57 °C, the half-life of the 4-methylbenzyl substrate **27b** at the same temperature was 0.8 min, and methoxy-substituted substrate **27c** could not be isolated at room temperature, having completely rearranged to indanone **28c** upon warming of the KO*t*-Bu elimination reaction mixture from −78 °C to ambient temperature. In contrast, the 4-trifluoromethylbenzyl substrate **27d** displayed a half-life of 13.3 min at 57 °C. These results suggest the development of charge deficiency (either radical or cation) at the benzylic carbon atom during the rearrangement. A similar study of the rates of reaction of substrates with various alkyne substituents (**27f−h**) was also informative. Compared with the parent unsubstituted phenylalkynyl ether **27a** ($t_{1/2}$ = 4.8 min), (4-methylphenyl)alkynyl ether **27f** rearranged with a half-life of 3.6 min; however, (4-trifluoromethylphenyl)alkynyl ether **27h** displayed a half-life of 4.6 min, indicating a slightly *faster* reaction than with the parent ether. Once again, the (4-methoxyphenyl)-alkynyl ether **27g** had completely rearranged to **28g** upon reaching room temperature after generation at −78 °C. These results are consistent with a change in mechanism upon proceeding from electron-donating to electron-withdrawing substituents on the aromatic unit of the alkynyl ether moiety, with a radical mechanism likely operative for the former substrates (pathway A) and a polar mechanism for the latter (pathway B).

α-Substituted benzyl alkynyl ethers **30** can also be prepared from the corresponding α-alkoxy ketones **29** via elimination of the derived enol triflates (Scheme 11). Rearrangement and 5-exo-dig cyclization under thermal conditions gave rise to 1,3-disubstituted 2-indanones with low to moderate diastereoselectivities for substrates containing α-methyl, α-butyl, and α-isopropyl groups. Only in the case of α-*tert*-butylbenzyl alkynyl ether was the rearrangement stereoselective, providing indanone **30d** with a >95:5 syn:anti ratio in 69% yield. It is likely that the bulky *tert*-butyl group prefers to be anti to the ketene unit in the nonaromatic intermediate; 5-exo-dig cyclization followed by syn-1,2-proton migration to the enolate carbon atom would then provide the product with the observed syn stereochemistry.

The substituted indanones prepared in this manner can be readily converted into substituted indenes, which are important building blocks for the synthesis of biologically active pharmaceutical agents.[23] Thus, benzyl alkynyl ethers are useful reagents in organic synthesis because their [3,3]-sigmatropic rearrangement and intramolecular cyclization reactions take place under mild conditions and allow the formation of complex indanone products that would be difficult to access by other synthetic methods.

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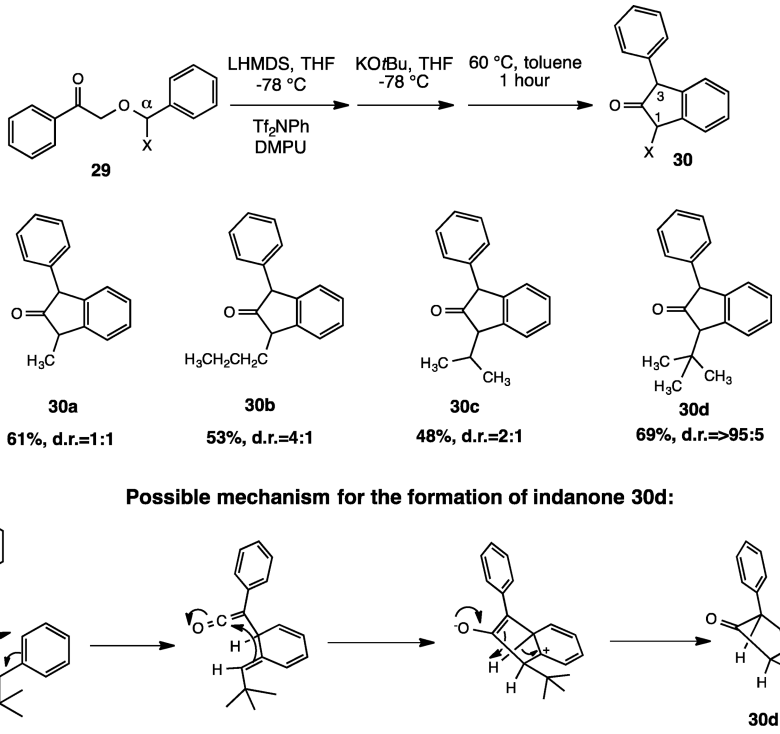
Scheme 11. Rearrangement Reactions of α-Substituted Benzyl Alkynyl Ethers

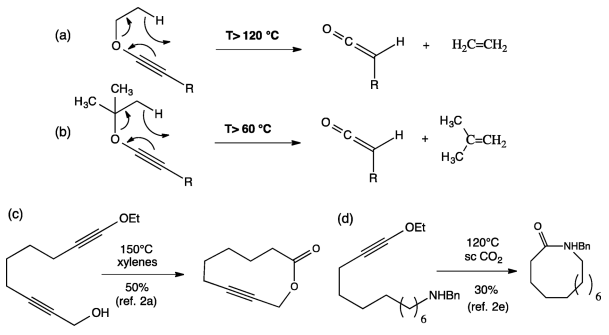


4. THERMAL RETRO-ENE/[2 + 2] CYCLOADDITION REACTIONS OF *tert*-BUTYL ALKYNYL ETHERS

Ketene intermediates are commonplace in the sigmatropic rearrangement chemistry of allyl and benzyl alkynyl ethers. It has been shown that ketenes also undergo a facile [2 + 2] cycloaddition with alkenes to form cyclobutanones,[24] and the intramolecular variant of this process has been studied extensively by the groups of Marko,[25] Snider,[26] and Brady.[27] However, the ketene intermediates utilized for these [2 + 2] cycloaddition reactions are most frequently generated from the corresponding acid chlorides by treatment with tertiary amines. The instability and moisture sensitivity of acid chlorides represents a potential drawback of this method, as well as the requirement of employing triethylamine for base-sensitive substrates.

In their pioneering studies, Ficini[29] and Arens[30] demonstrated that ethoxyacetylenes extrude ethylene gas at temperatures in excess of 100 °C to form aldoketenes, which either undergo dimerization reactions or can be trapped by nucleophiles to form carboxylic acid derivatives (Scheme 12). *tert*-Butyl alkynyl ethers undergo the retro-ene process with liberation of isobutylene gas at significantly lower temperatures,[1a] a reaction that has been utilized for the synthesis of lactones, lactams, amides, and cyclic imides.[2] It was reasoned that alkene-tethered *tert*-butyl ynol ethers could similarly be utilized for the synthesis of cyclobutanones via intramolecular [2 + 2] cycloaddition of the thermally generated aldoketene intermediate.[28]

Scheme 12. Thermal Ketene Generation/Intramolecular Trapping Reactions of Ynol Ethers



tert-Butyl ynol ethers can be prepared by the protocol of Danheiser[2e] from *tert*-butyl 1,2-dichlorovinyl ether **31** by treatment with excess butyllithium and trapping with aldehyde, imine, or alkyl halide electrophiles; subsequent reaction of the propargylic alcohol or sulfonamine intermediates with allylic halides or sulfonate esters under basic conditions then furnishes the ene−ynol ether substrates (**33**) for study (Scheme 13).

Heating substrates **33** in toluene at 90 °C for 1−3 h gave high yields of cyclobutanone-fused carbo- and heterocyclic ring systems with high diastereoselectivities for substrates bearing sterically demanding substituents (*i*-Pr, **34c**; *t*-Bu, **34d**, **34e**) in the ene−ynol ether tether. Two-dimensional NMR spectroscopy indicated that the major diastereomer formed in all cases possesses the 2,3-*syn*, 2,5-*syn* stereochemistry (cf. **34a**), in accord with literature precedent for similar ketene−olefin cycloadditions.[25−27] It is likely that a substrate conformer in which the C5 group adopts a pseudoequatorial orientation in the transition state for [2 + 2] cycloaddition gives rise to the observed stereochemistry.

Interestingly, it was also found that unprotected alcohol **35a** (Scheme 14) underwent the retro-ene/[2 + 2] cycloaddition process to furnish cyclobutanone **36a** in moderate yield but with high (>20:1) diastereoselectivity (compare **35b** → **36b**, 70% yield, dr = 2:1), perhaps indicating an interaction between the hydroxyl proton and the π systems of the ketene or alkene during the transition state for [2 + 2] cycloaddition. In this example, the process represents an advantage over other methods for ketene

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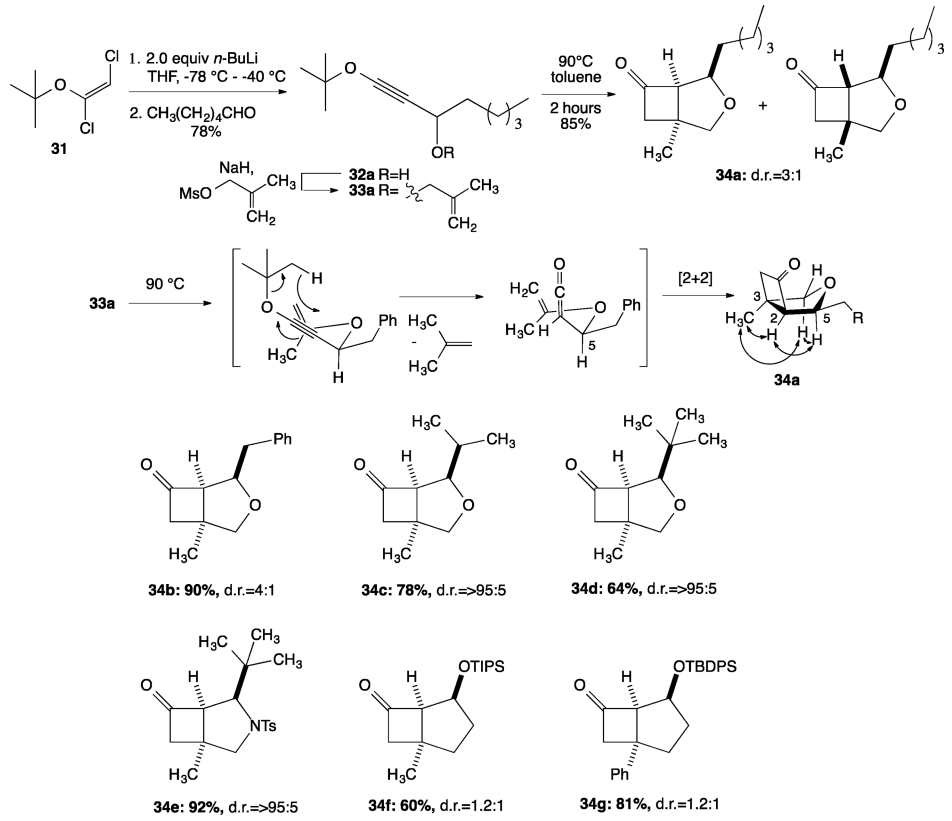
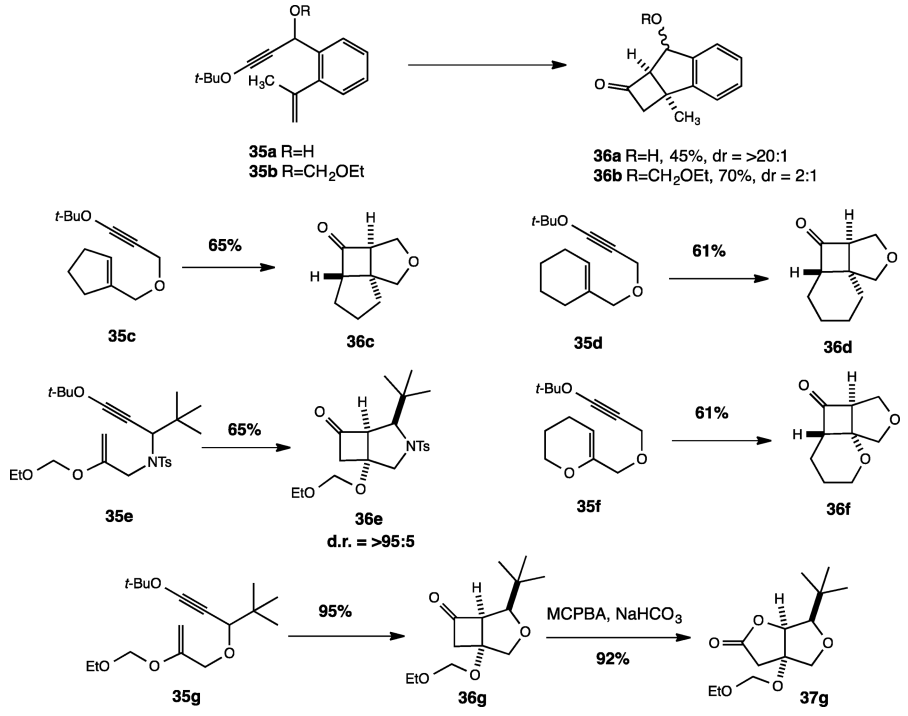
Scheme 13. Thermal Retro-Ene/[2 + 2] Cycloaddition of Alkene-Tethered Ynol Ethers



Scheme 14. Cycloadditions of Substrates Bearing Alcohols, Trisubstituted Alkenes, and Enol Ethers



generation involving acid chlorides, since hydroxyl-bearing substrates would be prone to inter/intramolecular esterification reactions under basic conditions. Furthermore, both trisubstituted alkenes and enol ethers could be employed efficiently in the [2 + 2] cycloaddition reaction, furnishing fused tricyclic compounds (e.g., **36b−d**) and donor−acceptor cyclobutanones (**36e−g**) in good yields.

The cyclobutanone products can be easily transformed into lactones by chemoselective oxidation with MCPBA to furnish synthetically useful cis-fused 5,5-ring systems such as **37g**.

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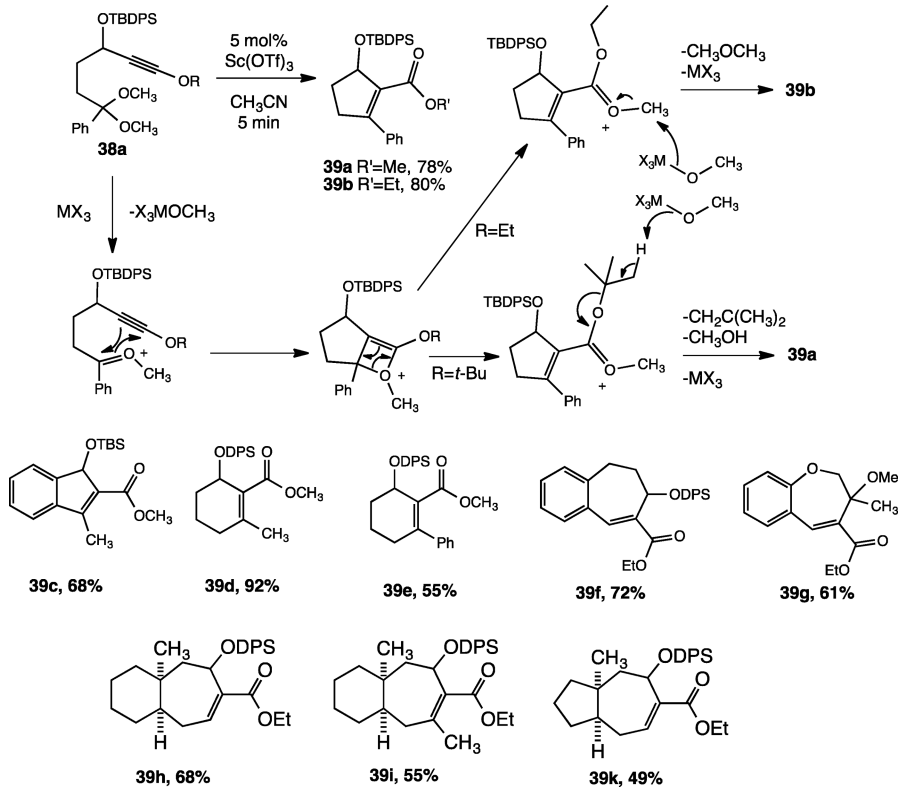
Scheme 15. Synthesis of Alkoxycycloalkene Carboxylates from Ynol Ether−Acetals



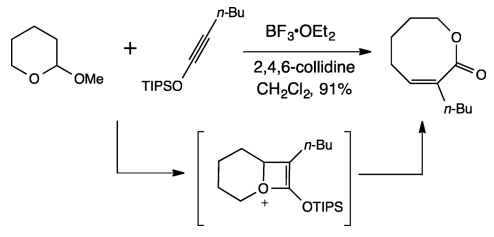
The thermal retro-ene/intramolecular [2 + 2] cycloaddition reaction of ene−ynol ethers thus represents a practical and useful alternative to currently available methods for the synthesis of fused cyclobutanones.

5. INTRAMOLECULAR LEWIS ACID-CATALYZED YNOL ETHER−ACETAL CONDENSATION

In an effort to extend the retro-ene/[2 + 2] cycloaddition reaction to the synthesis of β-lactones and lactams by thermolysis of carbonyl- and imine-tethered ynol ethers, it was discovered that attempted deprotection of the ynol ether−acetal precursors led to the formation of alkoxycycloalkene carboxylates instead of the desired carbonyl compounds.[31] For example, treatment of acetal **38a** with catalytic amounts of I_2 in acetone gave methyl ester **39a** in 45% yield; in a similar manner, treatment of **38a** with 5 mol % $Sc(OTf)_3$ in acetonitrile gave **39a** in 78% yield (Scheme 15). Other effective Lewis acid promoters of this intramolecular condensation reaction were TMSOTf (CH_2Cl_2, −78 °C, 70% yield of **39a**) and $In(OTf)_3$ (CH_3CN, rt, 50% yield of **39a**). A variety of five-, six, and seven-membered alkoxycycloalkane carboxylates could be prepared efficiently from ethyl- or *tert*-butyl ynol ether−acetals using 5 mol % $Sc(OTf)_3$ as a promoter in acetonitrile. A possible mechanistic pathway for this process might involve Lewis acid coordination of the acetal oxygen atom followed by ionization and ynol ether−oxonium ion metathesis. For *tert*-butyl ynol ether substrates, loss of isobutylene from the ensuing oxocarbenium ion would furnish the observed methyl ester product; for ethyl ynol ethers, S_N2-like cleavage at the oxocarbenium methyl group would furnish ethyl ester products.

This methodology allows the rapid preparation of complex 5,7- and 6,7-ring systems reminiscent of those present in sesquiterpene natural products. It affords protected hydroxycycloalkene carboxylates that may undergo further stereoselective transformations such as allylic substitution or Michael addition reactions, allowing the introduction of carbon substituents β to the ester functional group.[32] An intermolecular variant of this process using triisopropylsilyl ynol ethers and in situ-generated cyclic oxonium ions has recently been developed Zhao, Li, and Sun[33] for the synthesis of medium- and large-ring lactones (Scheme 16).

Scheme 16. Synthesis of Medium- and Large-Ring Lactones from Silyl Ynol Ethers



6. TANDEM LEWIS ACID-PROMOTED REACTIONS OF ETHOXYACETYLENE, EPOXIDES/OXETANES, AND CARBONYL COMPOUNDS

α-Alkylidene, α-benzylidene, and α-methylene lactone moieties are found in many biologically active natural products possessing antitumor, antifungal, and antibacterial activities.[34] These motifs have been constructed by the condensation of lactone enolates with carbonyl compounds,[35a] by transition-metal-mediated lactonizations,[35b] or by Wittig-type reactions of phosphonate anions/phosphorus ylides and carbonyl compounds.[35c] It was envisioned that with 1-alkynyl ethers, a one-pot procedure for the synthesis of α-alkylidene and α-benzylidene lactones could be

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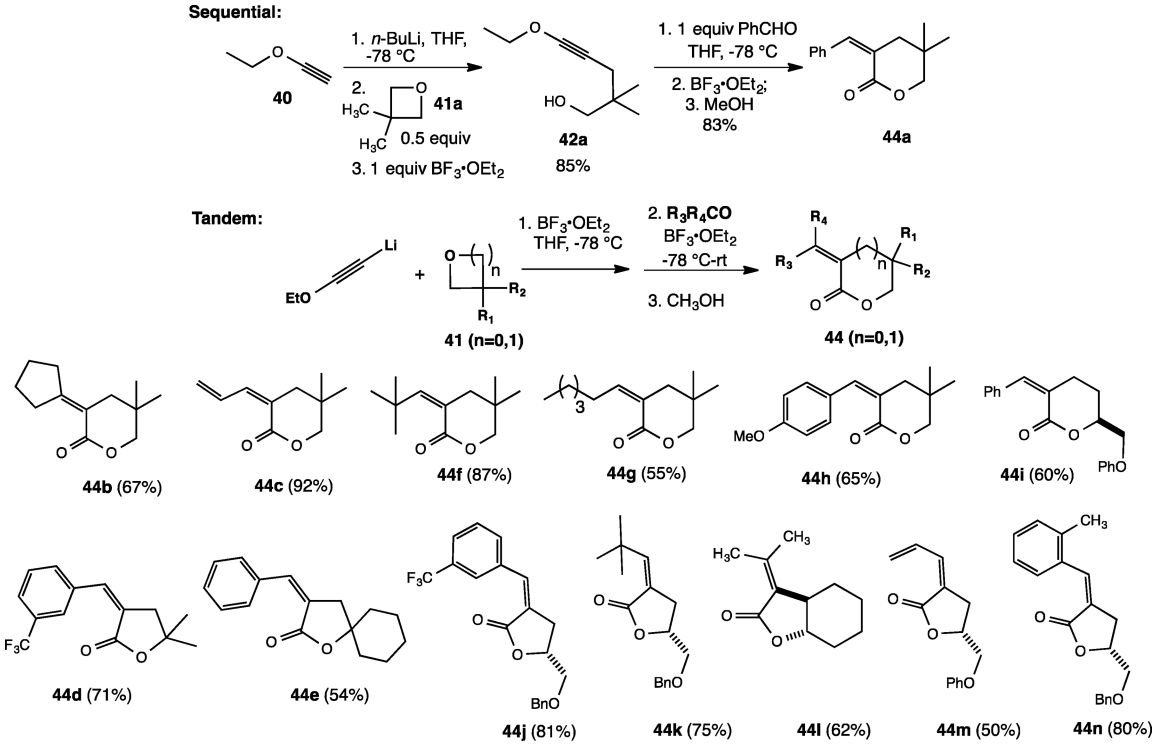
Scheme 17. Synthesis of α-Alkylidene and α-Benzylidene Lactones

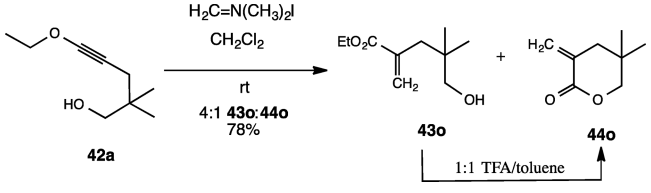


achieved using three separate Lewis acid-catalyzed reactions: an epoxide/oxetane ring opening with ethoxyacetylene, an ynol ether−carbonyl metathesis reaction, and a lactonization of a hydroxy ester. Indeed, it was found that $BF_3{\cdot}OEt_2$ is an efficient promoter of all three reactions, and high yields of unsaturated lactone products could be obtained in a single-flask procedure.[36] Combination of (ethoxyethynyl)lithium with epoxides or oxetanes in the presence of 1 equiv of $BF_3{\cdot}OEt_2$ gave rise to an isolable intermediate hydroxy−ynol ether (cf. **42a**, Scheme 17), which could be further combined with equimolar amounts of aldehyde or ketone and $BF_3{\cdot}OEt_2$ to produce an acyclic α-alkylidene or α-benzylidene ester (vide infra, **43**, Scheme 19); subsequent addition of methanol to the reaction mixture and stirring at room temperature gave rise to the expected lactone products **44** with virtually exclusive production of the (*Z*)-alkene stereoisomer.

A variety of mono- and disubstituted epoxides and oxetanes participate in this process, as well as electron-rich and electron-deficient aryl aldehydes, hindered and unhindered aliphatic aldehydes, cyclic and acylic ketones, and unsaturated aldehydes. α-Methylene lactones could also be prepared in a two-step sequence involving reaction of hydroxy−ynol ether **42a** with Eschenmoser's salt followed by stirring with TFA in toluene to effect lactonization, producing **44o** (Scheme 18).

From a mechanistic standpoint, combination of metalated ynol ether **40**·Li with **41a** and $BF_3{\cdot}OEt_2$ gives rise to intermediate

Scheme 18. Formation of α-Methylene Lactones



42a·BF_3Li, which then participates in metathesis with the added equivalent of carbonyl compound activated by a second equivalent of $BF_3{\cdot}OEt_2$ (Scheme 19). The *E*/*Z* mixture initially produced at the acyclic unsaturated ester stage then undergoes alkene *E*-to-*Z* isomerization and lactonization reactions facilitated by $BF_3{\cdot}OEt_2$ and the Brønsted acid formed when methanol is introduced into the reaction medium. Alkene isomerization may take place either before or after lactonization: whereas compound **43a** (reaction a) is isolated as a 2.2:1 mixture of *Z* and *E* alkene stereoisomers, indicating a fast lactonization process (facilitated by the *gem*-dimethyl effect) occurring prior to complete alkene isomerization, alcohol **43i** (reaction b) is formed as the *Z* isomer exclusively as a result of a slower lactonization process, allowing complete alkene *E*-to-*Z* isomerization of the acyclic enoate to take place under the acidic reaction conditions.

This tandem process accomplishes the formation of three carbon−carbon bonds and a ring in a single chemical transformation and stereoselectively affords (*Z*)-α-alkylidene and (*Z*)-α-benzylidene lactones. We are currently exploring the application of this concept to the synthesis of acyclic and cyclic Baylis−Hillman adducts by the tandem reaction of metalated ethoxyacetylene with sequentially added carbonyl compounds or dicarbonyl compounds in the presence of Lewis acid (Scheme 20).

7. CONCLUSION

1-Alkynyl ethers have been shown to participate in a variety of useful tandem bond-forming reactions that result in the construction of complex cyclic (lactone, cyclobutanone, indanone, alkoxycycloalkene carboxylate) and acyclic (γ,δ-unsaturated carboxylate) products that are useful as intermediates in organic synthesis. In addition, it may be envisioned that many of these products may be readily elaborated to provide natural substances of medicinal and biological import. It is thus hoped that this Account stimulates further interest in and research on the

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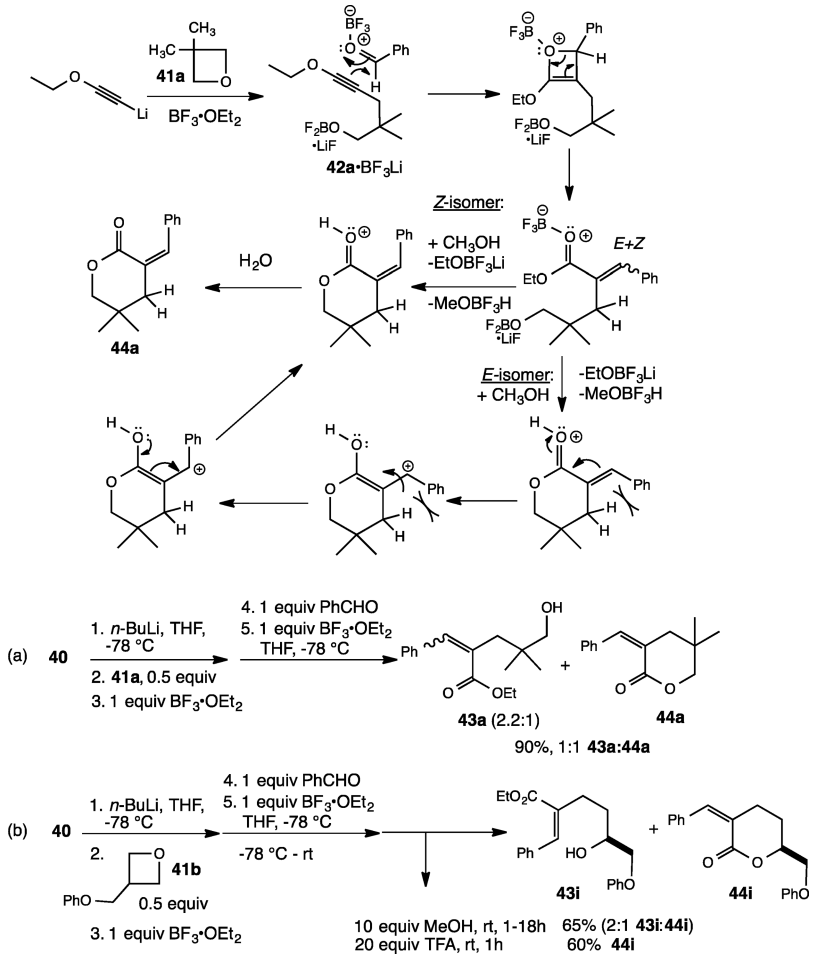
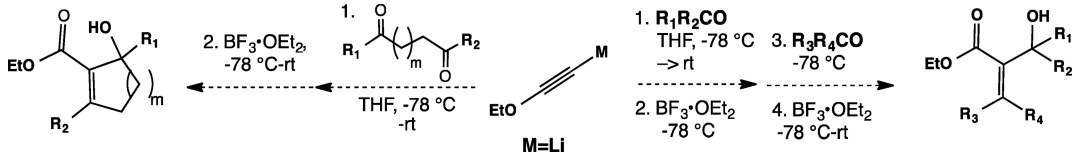
Scheme 19. Mechanistic Hypothesis for the Lewis Acid-Promoted Tandem Reaction



Scheme 20. Synthesis of Baylis–Hillman Adducts by Ynol Ether–Carbonyl Tandem Reactions



applications of ynol ethers for carbon–carbon bond formation in natural product synthesis.

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Notes

The authors declare no competing financial interest.

Biography

Thomas G. Minehan earned his B.A. in Chemistry from Columbia University (1992) and his Ph.D. in Chemistry from Harvard University (1998), working under the direction of Professor Yoshito Kishi. He then moved to California Institute of Technology to work with Professor Peter Dervan. In 2001, Professor Minehan began his independent academic career at Harvey Mudd College. In 2004, he moved to California State University, Northridge, where he is currently Professor of Chemistry. Professor Minehan is a synthetic organic chemist whose research program focuses on natural product synthesis and the development of new and efficient methods for carbon–carbon bond formation.

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