Tandem Bond-Forming Reactions of 1-Alkynyl Ethers.

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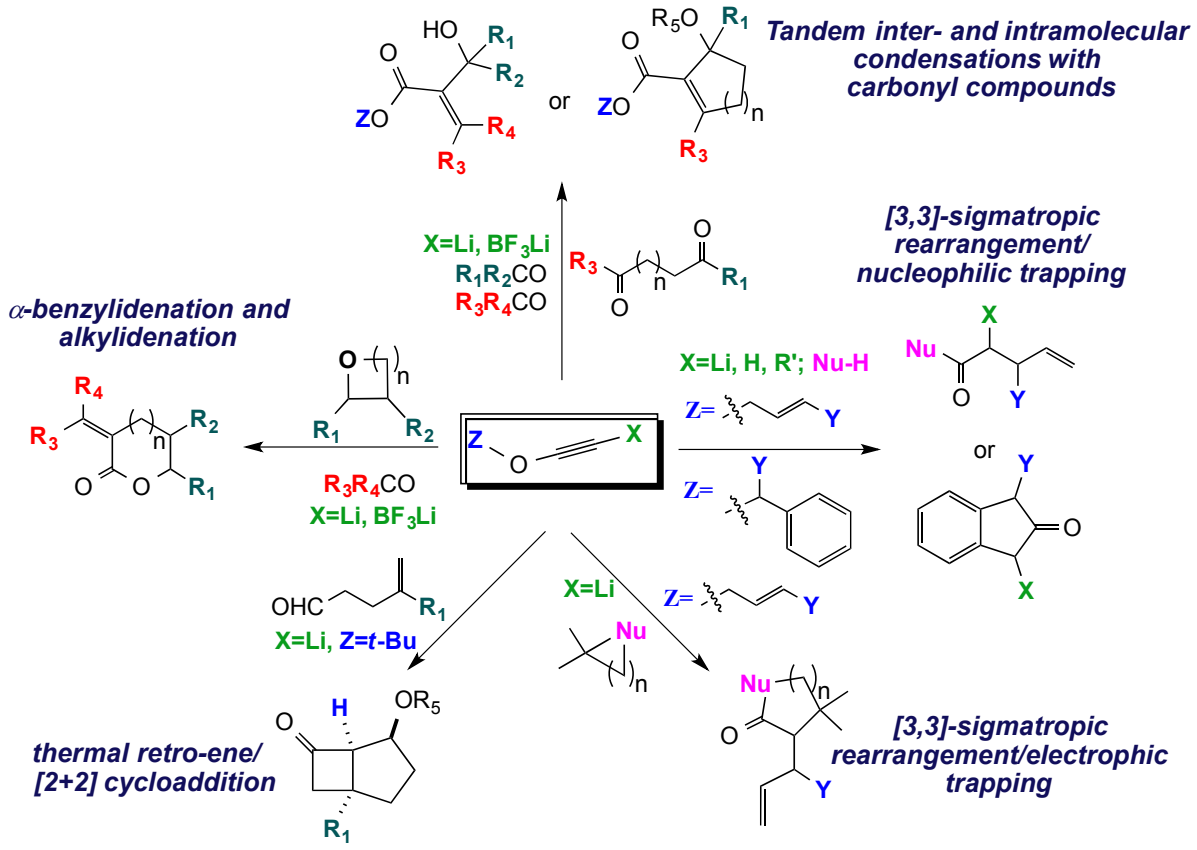
CONSPECTUS: Electron rich alkynes, such as ynamines, ynamides, and ynol ethers, are functional groups that possess significant potential in organic chemistry for the formation of carbon-carbon bonds. While the synthetic utility of ynamides has been expanded considerably recently, 1-alkynyl ethers, which possess many of the reactivity features of ynamides, have traditionally been far less investigated due to concerns about their stability. Like ynamides, ynol ethers are relatively unhindered to approach by functional groups present in the same or different molecules due to 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 °C 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 for employing 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 provide protected 5-, 6-, and 7-membered cyclic Baylis Hilman adducts efficiently. 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 and 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 will provide 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 C.1, Figure 1) and as a nucleophile (at C.2).[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 C.2 with an electrophile (El') and at C.1 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 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]

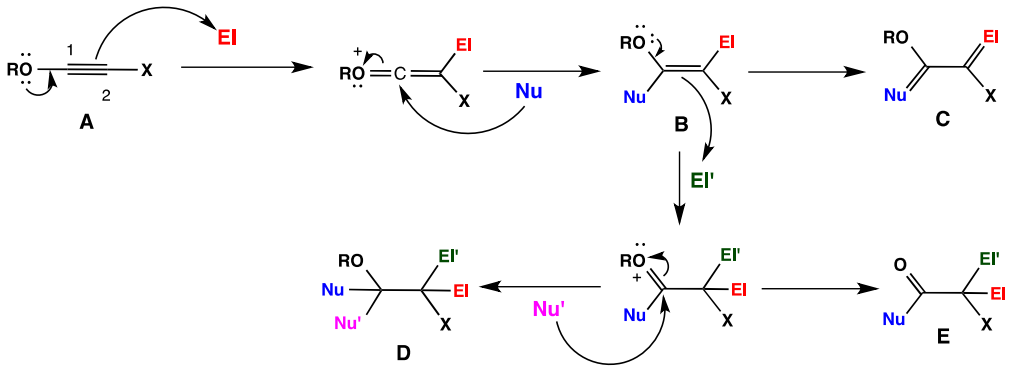


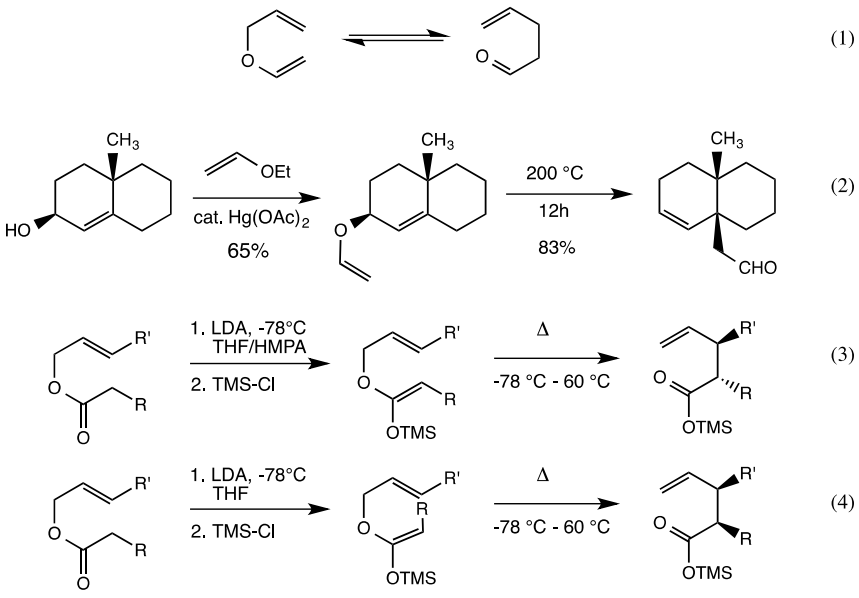
Figure 1. The reactivity of 1-alkynyl ethers.

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 build-up of molecular complexity.

1. [3,3]-SIGMATROPIC REARRANGEMENT OF ALLYL-ALKYNYL ETHERS

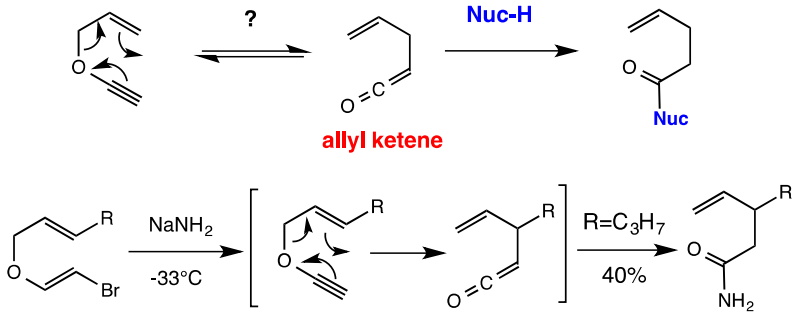
The [3,3]-sigmatropic rearrangement of allyl vinyl ethers (the Claisen rearrangement) is a

powerful method for the formation of carbon-carbon bonds.[6] In this process, a C-O sigma bond is broken and a C-C sigma 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 °C - 60 °C) and with predictable and high diastereoselectivities based on the control of the intermediate enol/enolate geometry (Scheme 1).[9]



Scheme 1. The Claisen rearrangement (1): thermal[7] (2) and Ireland-Claisen (3,4) variants.[9]

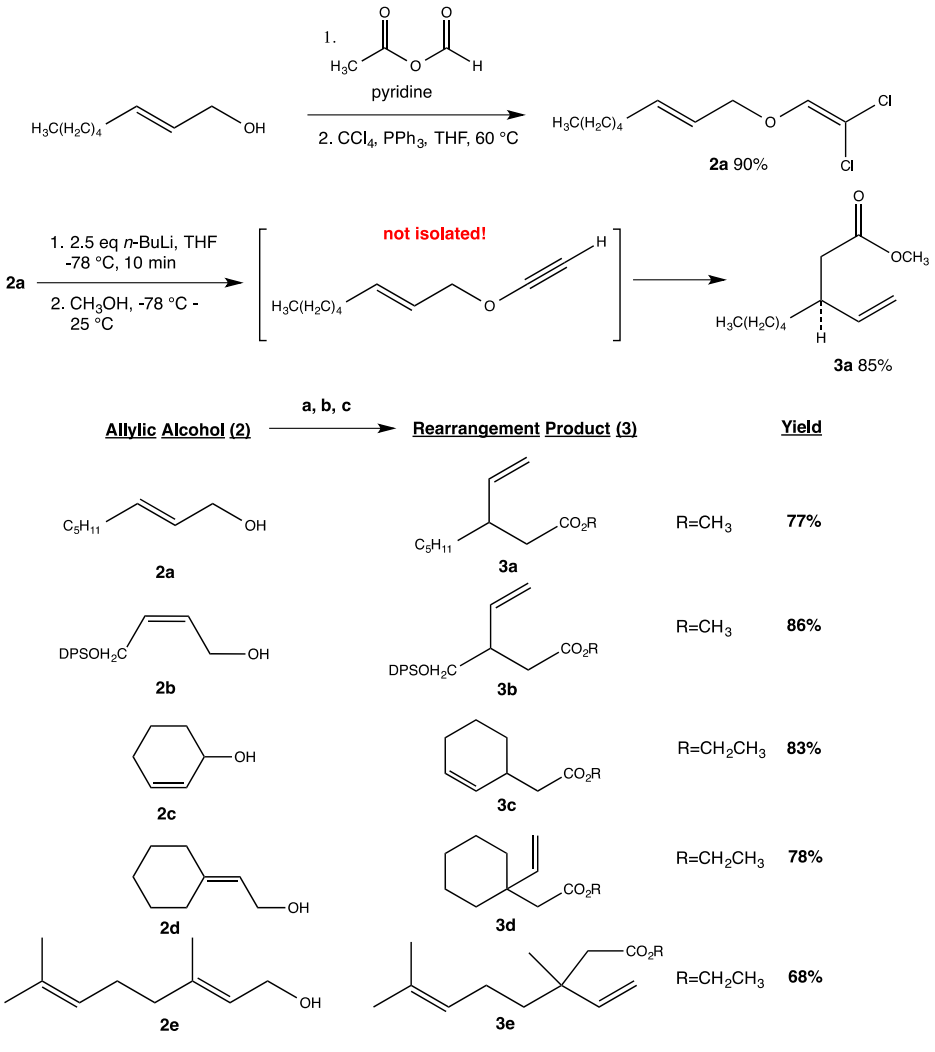
We initially were interested in investigating if allyl-1-alkynyl ethers would similarly participate in a Claisen-like [3,3]-sigmatropic process (Scheme 2). Once again, the exchange of a weaker alkene (C=C) bond for a stronger carbonyl (C=O) bond would provide the thermodynamic driving force for the rearrangement, 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 Schmidt[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] 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 trap 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.



Scheme 2. Allyl-alkynyl ether sigmatropy; Katzenellenbogen's study.[12]

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



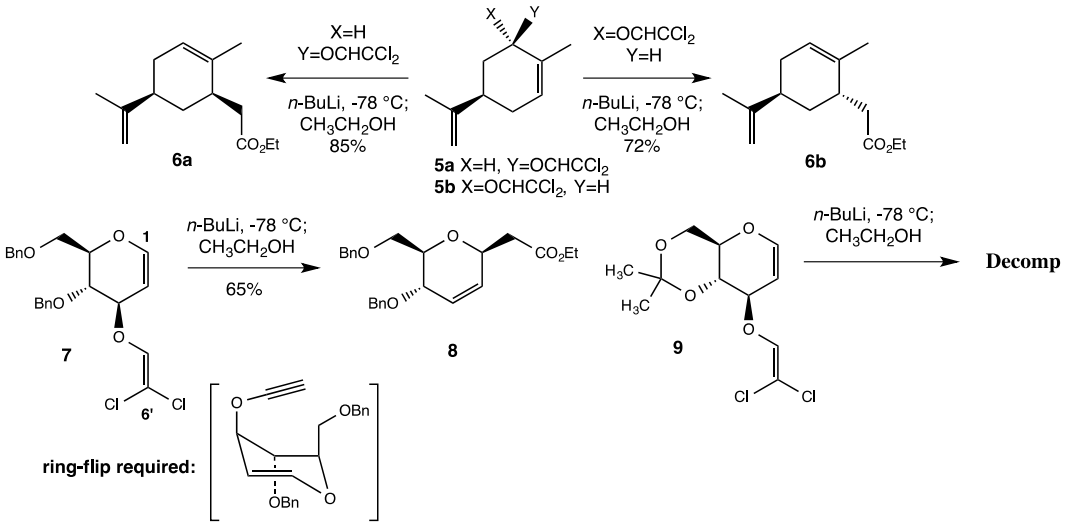
a. acetic formic anhydride, pyridine. b. PPh_3, CCl_4, THF. c. 2.2 eq *n*-BuLi, THF; ROH

Scheme 3. Preparation and *n*-BuLi-induced rearrangement of allyl-1,1-dichlorovinyl ethers.

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 <10% of the desired vinyl ethers being formed. 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 *n*-BuLi (-78 °C, 10 minutes), followed by reaction quench 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

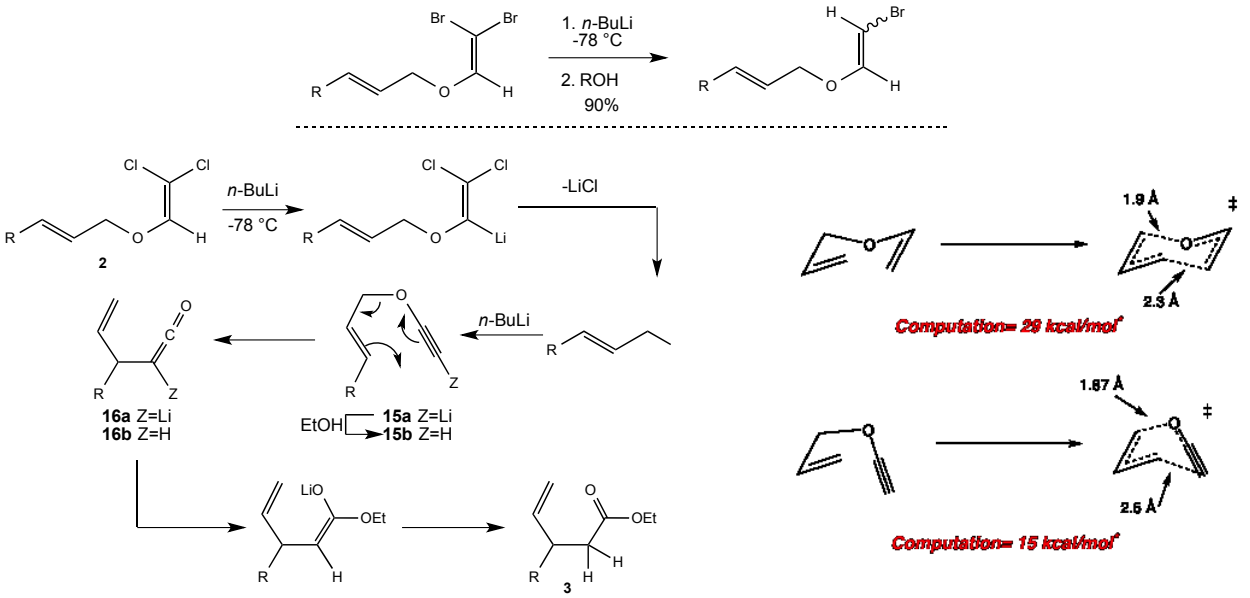
mixture was warmed to room temperature. Since the dichlorovinyl ether unit of **9** cannot access an axial conformation necessary to achieve close proximity of the reacting termini at C.1 and C.6', these results provide evidence for the existence of a pathway involving a cyclic transition state.



Scheme 4. Probing the stereospecificity of the [3,3]-sigmatropic rearrangement

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 >10% 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 vinyl ether deprotonation/chloride ion elimination 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]

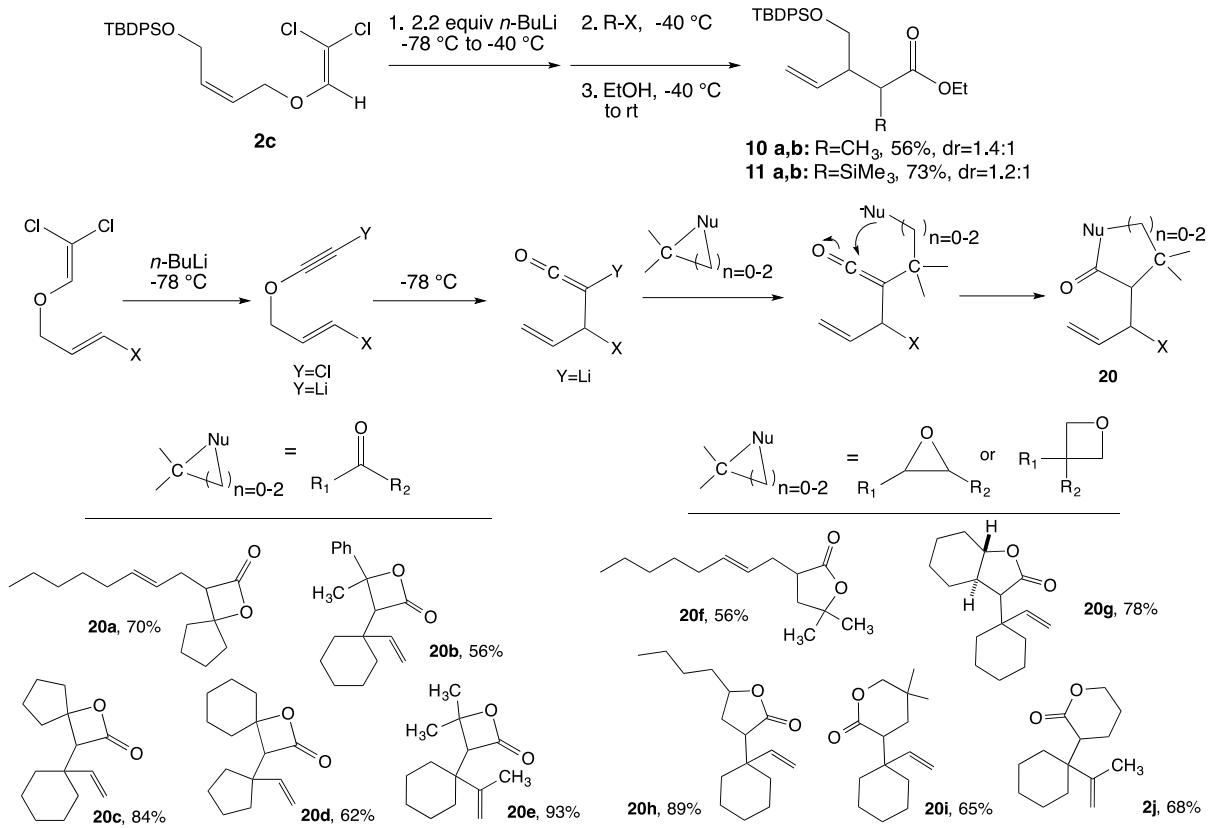
(**16a**) or via protonated acetylene (**15b**, formed after addition of the alcohol quenching agent) to produce allyl ketene **16b**. Reaction of the lithioketene or allyl ketene with alcohol would then provide the observed unsaturated ester product. An alternative means for preparing neutral allyl 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/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 as compared to its allyl vinyl ether counterpart.



Scheme 5. Proposed mechanism for the *n*-BuLi induced rearrangement of ethers **2**.

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

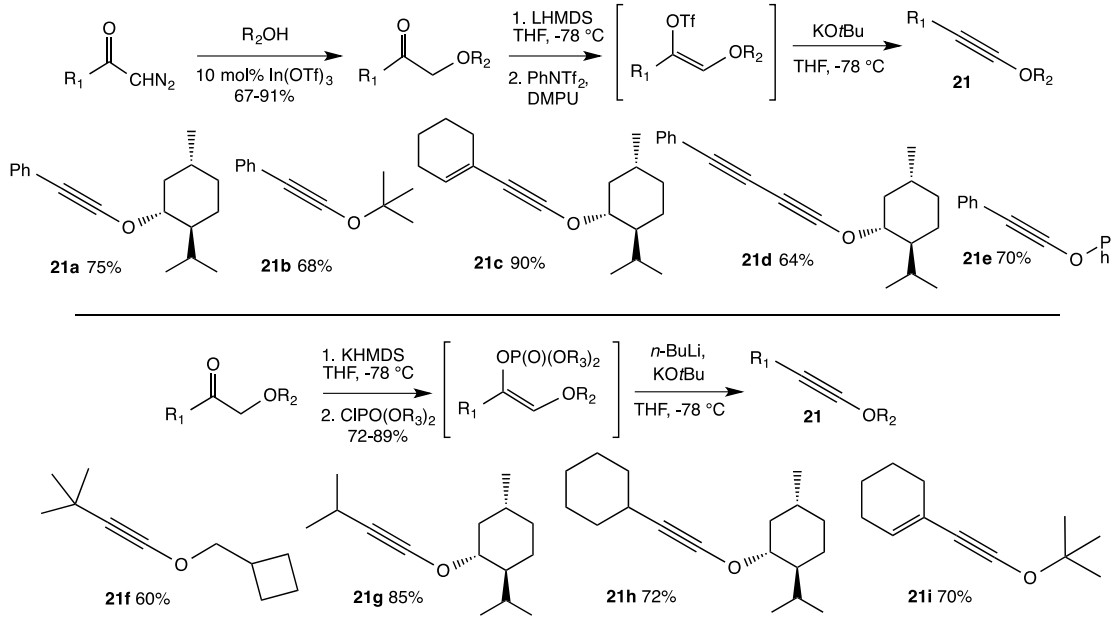
2c with *n*-BuLi at -78 °C, followed by methyl triflate or TMSCl (2 equiv) and then excess ethanol gave rise to α-substituted unsaturated esters in good yields, albeit in poor diastereoselectivity (Scheme 6). It was subsequently discovered that addition of symmetrical or unsymmetrical ketones to the 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•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 c□□□□□□□□□□□□□□□ to be prepared in a single-flask process from allyl-1,1-dichlorovinyl ethers.



Scheme 6. Electrophile trapping of the anionic rearrangement intermediate

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/$PhNTf_2$. It is likely that under the basic reaction conditions these enol triflates decompose *in situ* to 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).

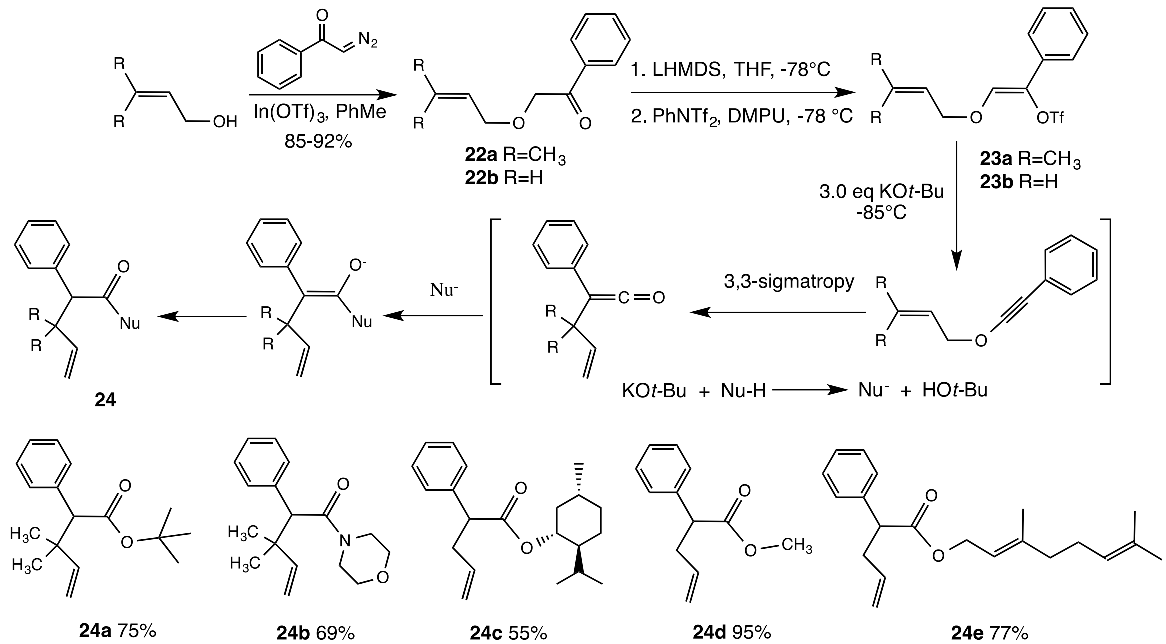


Scheme 7. Preparation of 1-alkynyl ethers from α-alkoxy ketones

With an alternative method for preparing alkynyl ethers in hand, we wished to explore if the [3,3] sigmatropic rearrangement of *in-situ* prepared neutral allyl alkynyl ethers 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 three equivalents of morpholine at -78 °C gave rise to amide **24b** (Scheme 8). Interestingly, while 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 only furnished the α-alkoxyketone **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 is 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 due to 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.



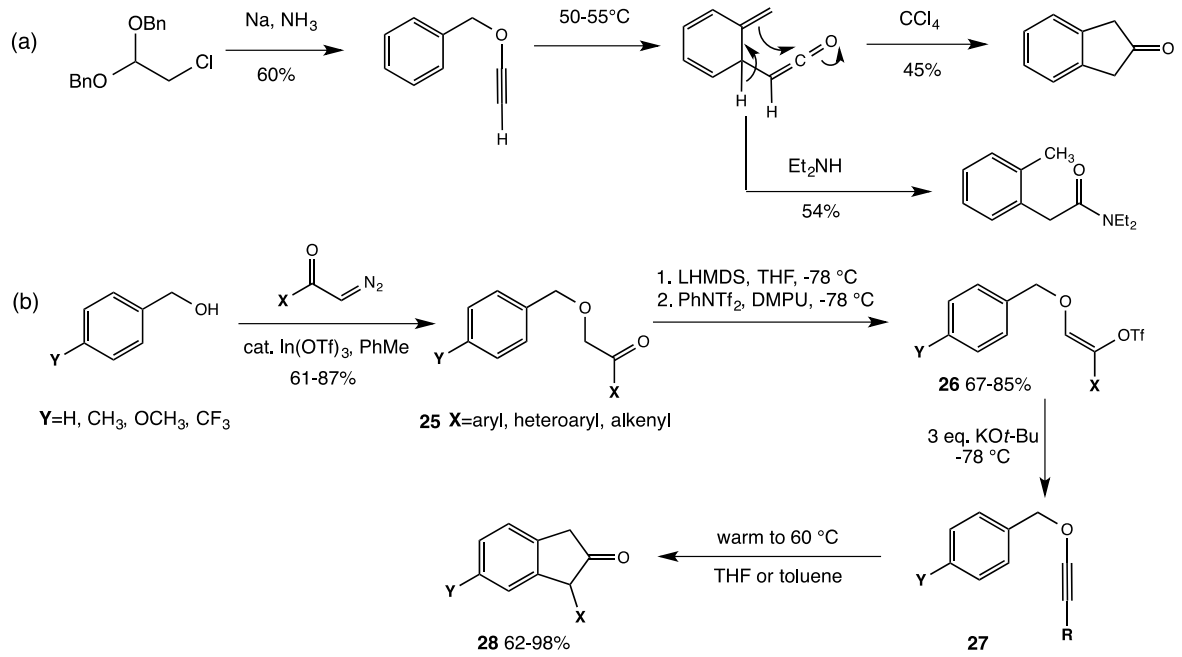
□□□e□□□**8**□□□□□□□□□□□□□□□□□□□□□□□□□□□□□□□□e□□ *via* KO*t*-Bu induced elimination of enol triflates.

2. [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 Schmidt.[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 non-aromatic allyl ketene intermediate that was either trapped with nucleophiles or underwent ring closure to furnish the observed products (a, Scheme 9).

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

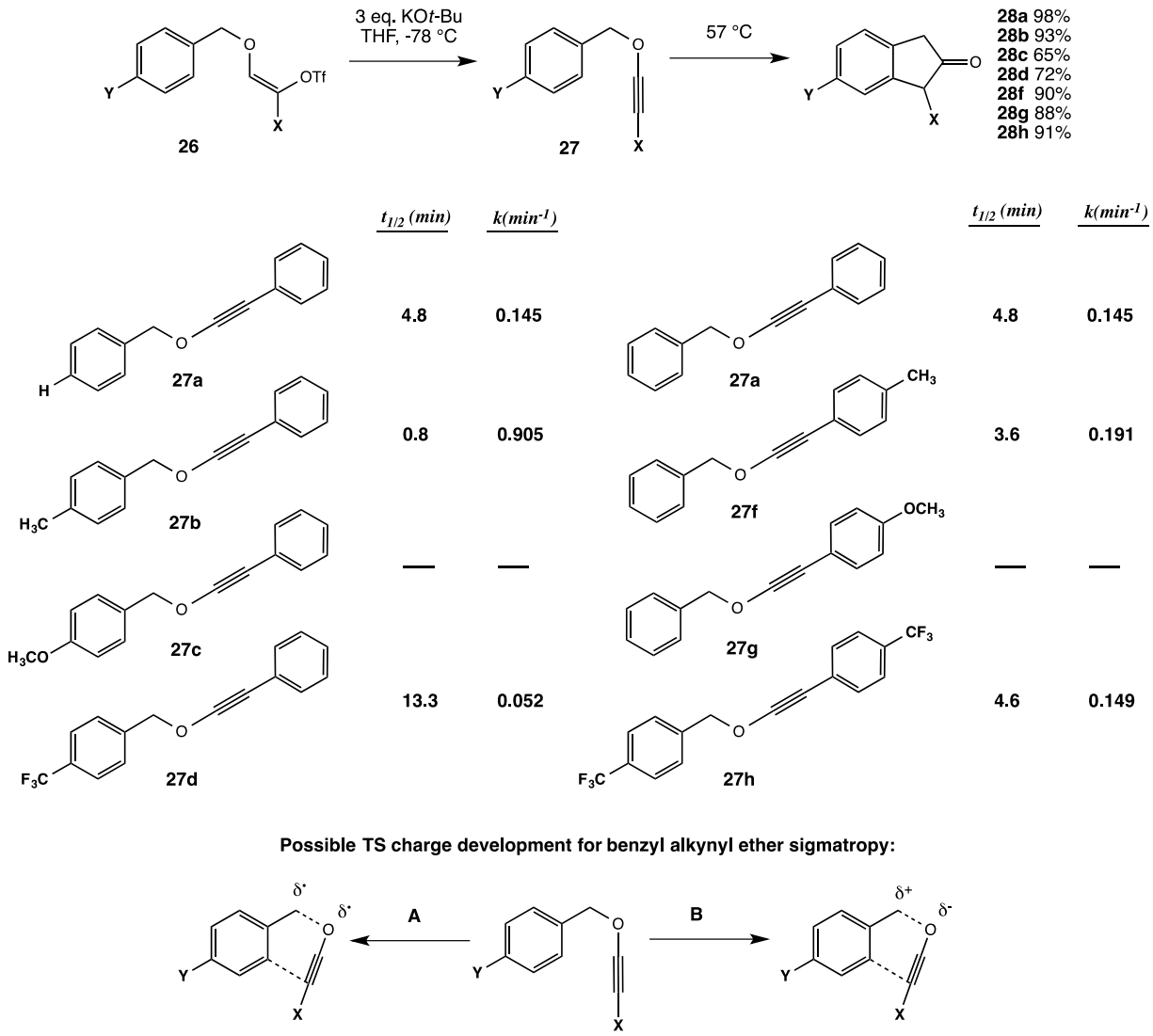
KO*t*-Bu in THF at -78°C to provide benzyl alkynyl ethers **27** (Scheme 9, equation b).[22] Simply heating these ethers in toluene at 60 °C for one hour induced rearrangement to 2-indanones **28** in high yields



Scheme 9. Previous (a) and current (b) examples of benzyl alkynyl ether sigmatropy

Studying the rates of rearrangement of substituted alkynyl ether substrates **27a**-**27d** 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 minutes at 57 °C, the half-life of the 4-methylbenzyl substrate **27b** at the same temperature was 0.8 minutes, and methoxy-substituted substrate **27c** could not be isolated at room temperature, having completely rearranged to indanone **28c** upon warming the KO*t*-Bu elimination reaction from -78 °C to ambient. In contrast, the 4-trifluoromethyl-benzyl substrate **27d** displayed a half-life of 13.3 minutes at 57 °C. These results suggest the development of charge deficiency (either radical or cation) at the benzylic carbon atom during the rearrangement.

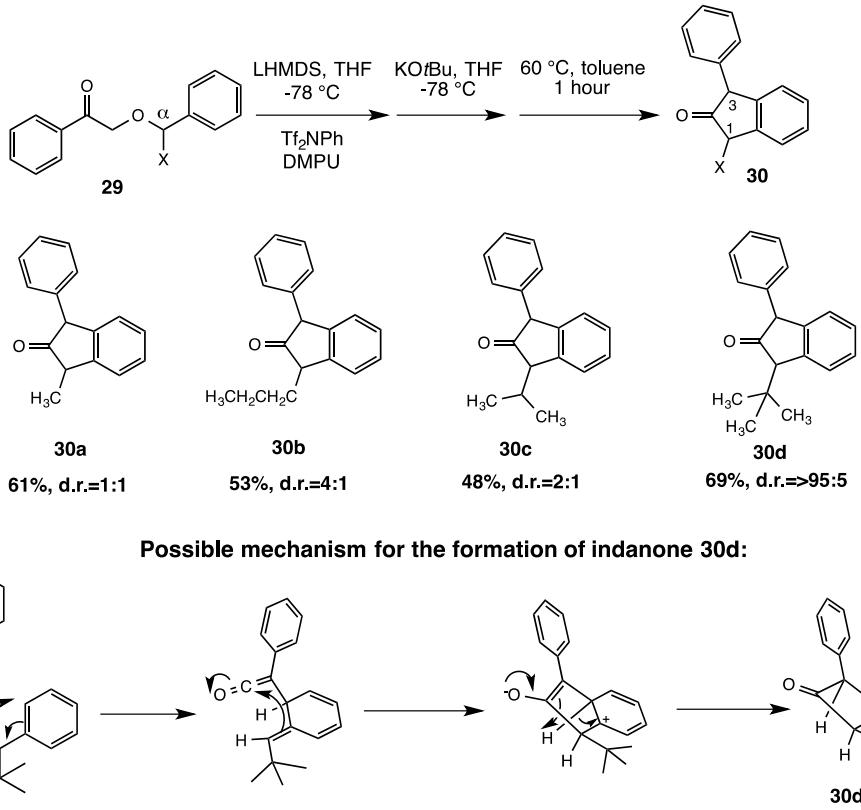
A similar study of the rates of reaction of substrates with various alkyne substituents (**27f**-**27h**) was also informative. Compared to the parent unsubstituted phenylalkynyl ether **27a** ($t_{1/2}$=4.8 minutes), 4-methyl-phenylalkynyl ether **27f** rearranged with a half life of 3.6 minutes; however, 4-trifluoromethyl-phenylalkynyl ether **27h** displayed a half life of 4.6 minutes, slightly *faster* than 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).



Scheme 10. Kinetic data for rearrangement of substituted benzyl alkynyl ethers

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-disustituted 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*-butyl benzyl alkynyl ether was rearrangement stereoselective, providing indanone **30d** with a >95:5 ratio of *syn*:*anti* isomers in 69 % yield. It is

likely that the bulky *tert*-butyl group prefers to be *anti* to the ketene unit in the non-aromatic 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.

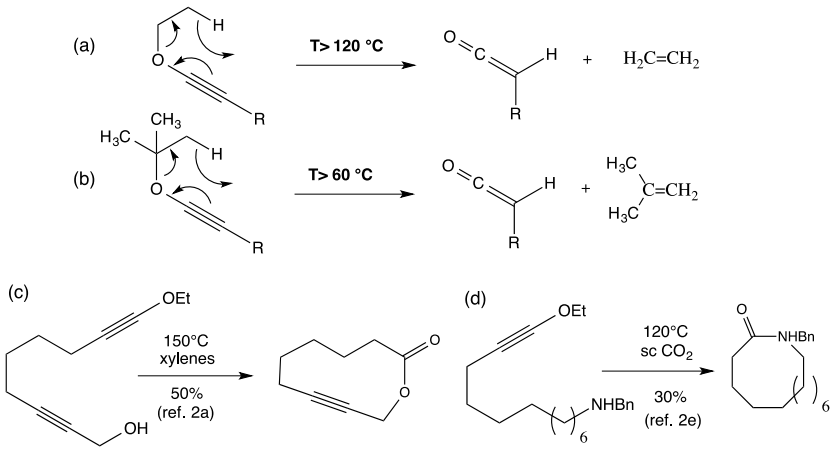


Scheme 11. Rearrangement reactions of α-substituted benzyl alkynyl ethers

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.

3. 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 for employing triethylamine for base-sensitive substrates.

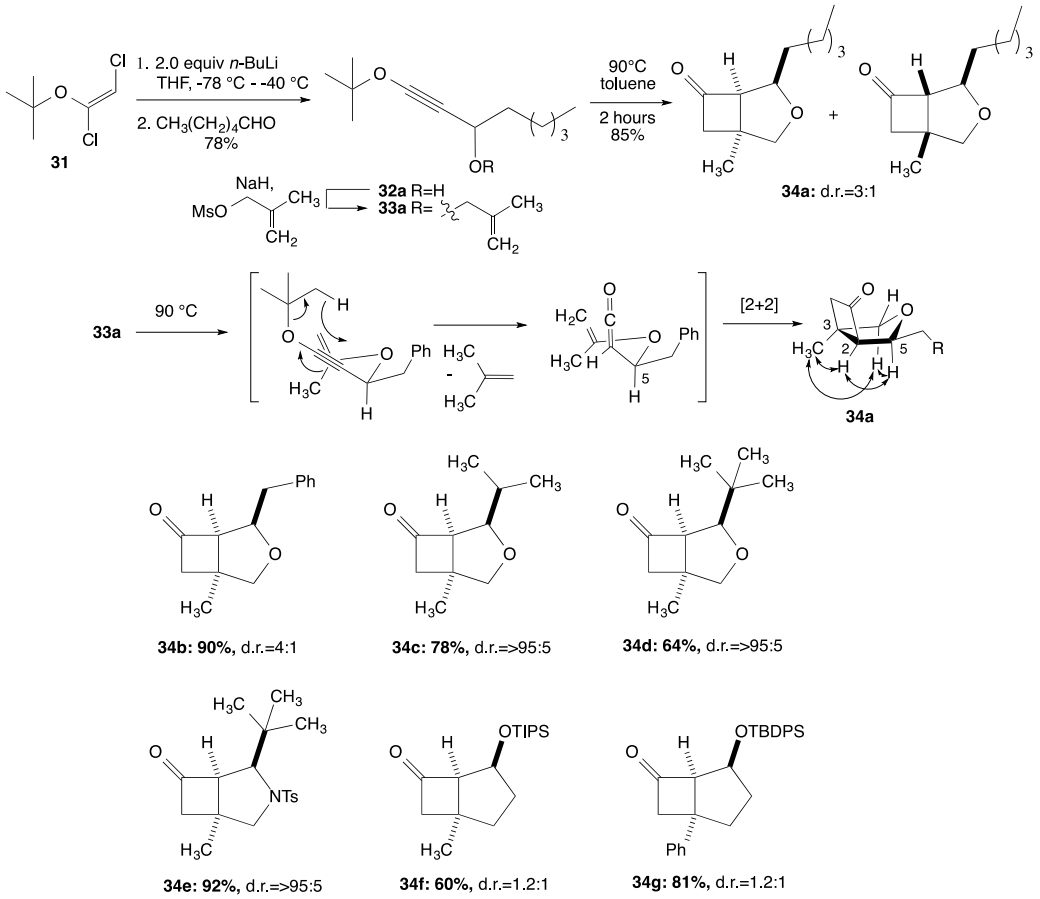


Scheme 12. Thermal ketene generation/intramolecular trapping reactions of ynol ethers.

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

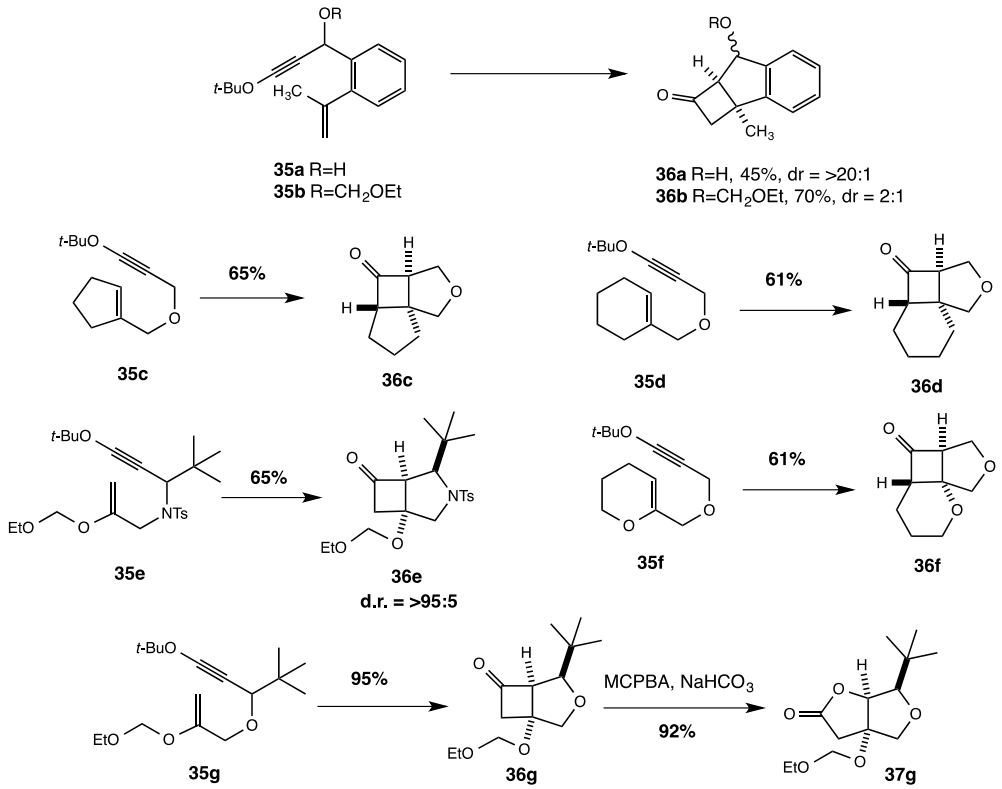
synthesis of lactones, lactams, amides, and cyclic imides.[2] It was reasoned that alkene-tethered *tert*-butyl ynol ethers could similarly be utilized for the synthesis of cyclobutanones via intramolecular [2+2] cycloaddition of the thermally generated aldoketene intermediate.[28]

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).



Scheme 13. Thermal retro-ene/[2+2] cycloaddition of alkene-tethered ynol ethers

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 C.5 group adopts a pseudoequatorial orientation in the transition state for [2+2] cycloaddition gives rise to the observed stereochemistry.



Scheme 14. Cycloadditions of substrates bearing alcohols, trisubstituted alkenes, and enol ethers.

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

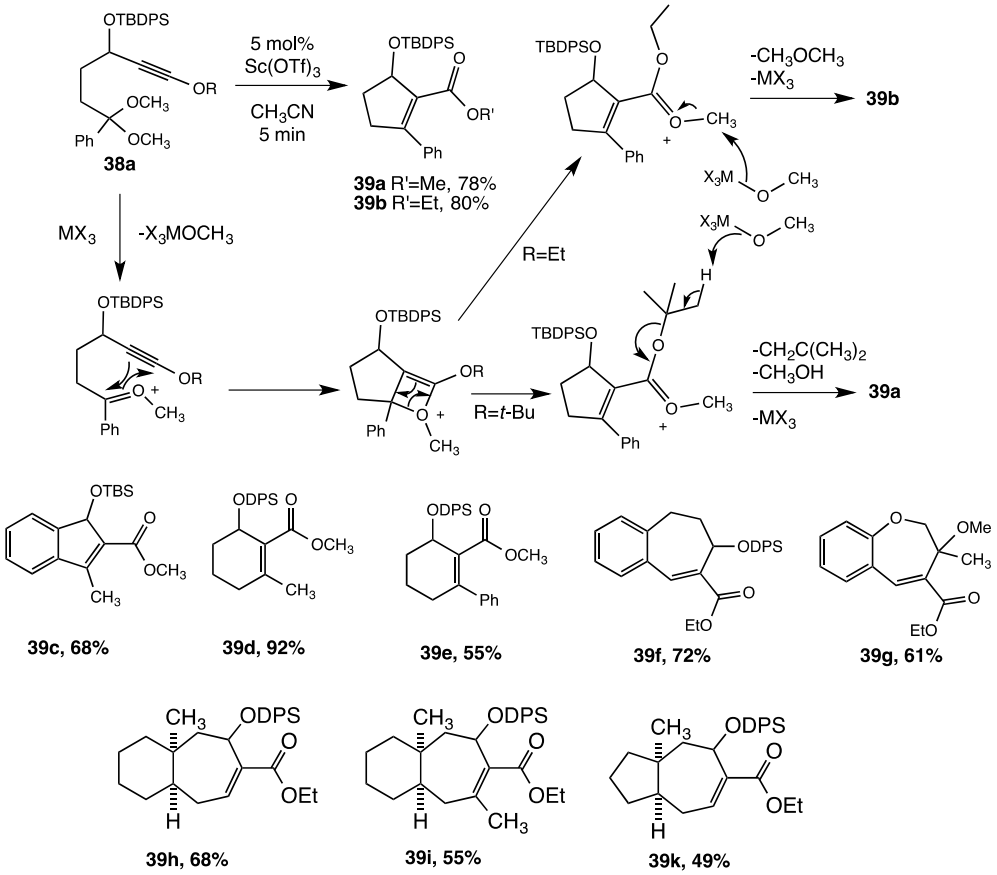
interaction between the hydroxyl proton and the π systems of the ketene or alkene during the transition state for [2+2] cycloaddition. In this example, the process represents an advantage over other methods for ketene generation involving acid chlorides, since hydroxyl-bearing substrates would be prone 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 (eg, **36b**, **36c**, **36d**) and donor-acceptor cyclobutanones (**36e**, **36f**, **36g**) 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**. 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.

4. INTRAMOLECULAR LEWIS ACID-CATALYZED YNOL ETHER-ACETAL CONDENSATION

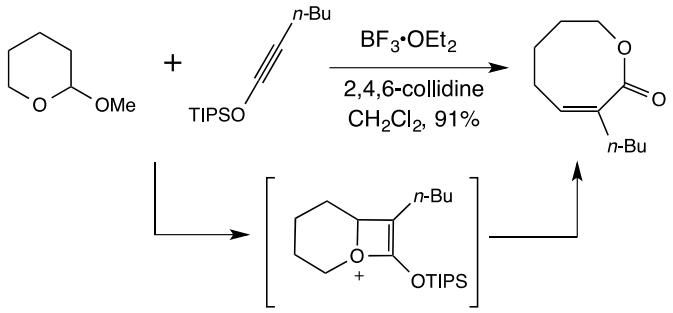
In an effort to extend the retro-ene/[2+2] cycloaddition reaction to the synthesis of β-lactones and lactams by thermolysis of carbonyl- and imine-tethered ynol ethers, it was discovered that attempted deprotection of the ynol ether-acetal precursors led to the formation of alkoxycycloalkene carboxylates 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 78% of **39a** (Scheme 15). Other effective Lewis acid promoters of this intramolecular condensation reaction were TMSOTf (CH_2Cl_2, -78 °C, 70% **39a**) and $In(OTf)_3$ (CH_3CN, rt, 50% **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, a 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.



Scheme 15. Synthesis of alkoxycycloalkene carboxylates from ynol ether-acetals

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).

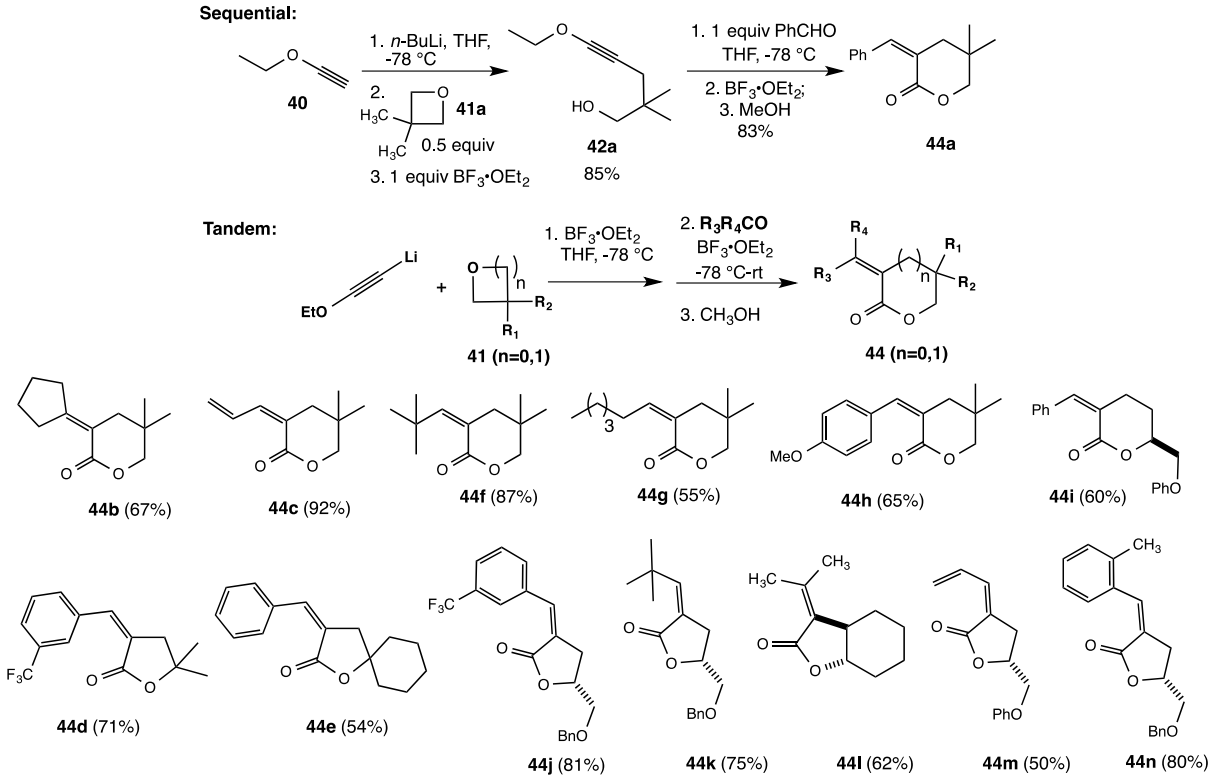


Scheme 16. Synthesis of medium and large ring lactones from silyl ynol ethers.

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

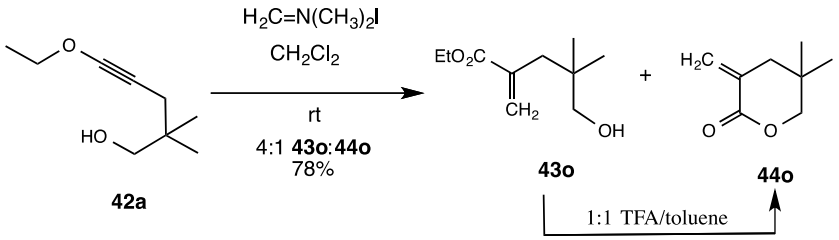
α-Alkylidene, α-benzylidene, and α-methylene lactone moieties are found in many biologically active natural products possessing antitumor, antifungal, and antibacterial activities.[34] This motif has been constructed by the condensation of lactone enolates with carbonyl compounds,[35a] by transition metal-mediated lactonizations,[35b] or by Wittig-type reactions of phosphonate anions/phosphorous ylides and carbonyl compounds.[35c] Utilizing 1-alkynyl ethers, it was envisioned that a one-pot procedure for the synthesis of α-alkylidene and α-benzylidene lactones could be 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•OEt_2 was an efficient promoter for 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 one equivalent of BF_3•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•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 virtual exclusive production of the *Z* –alkene stereoisomer.



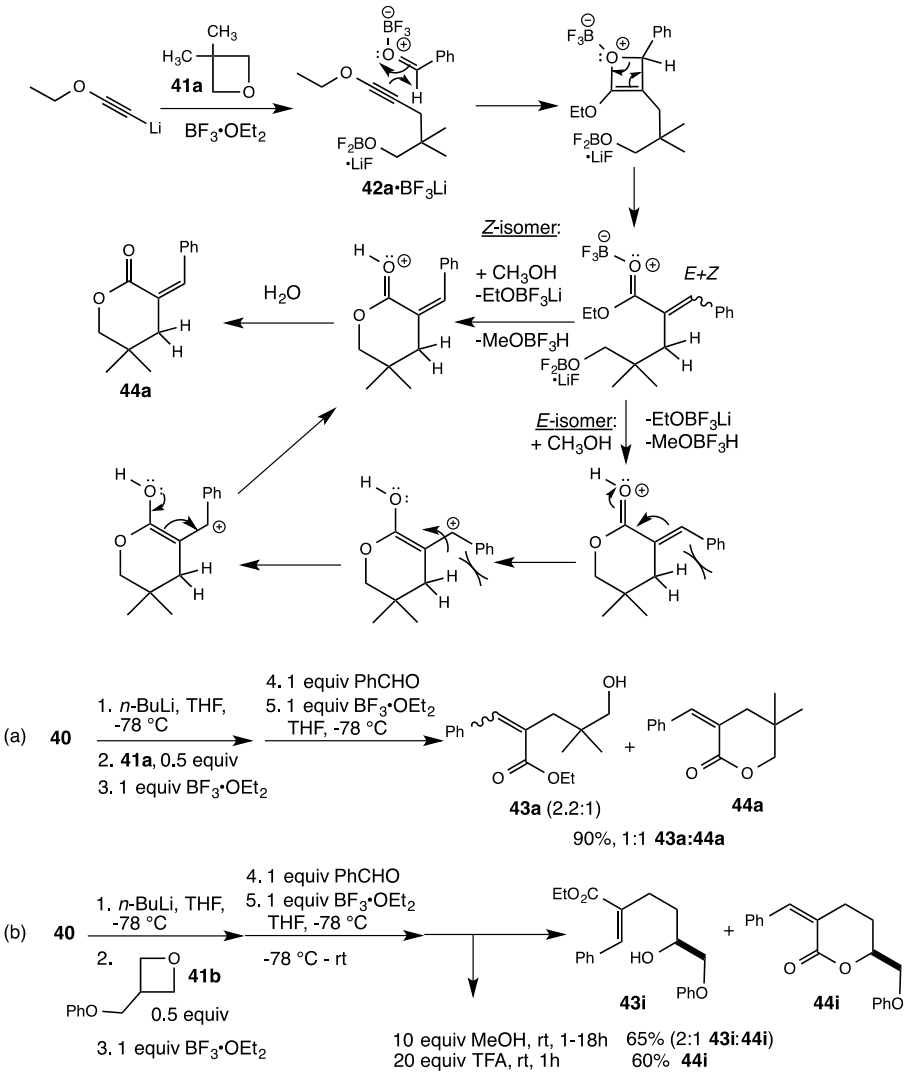
Scheme 17. Synthesis of α-alkylidene and α-benzylidene lactones.

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 hydroxyl-ynol ether **42a** with Eschenmoser's salt, followed by stirring with TFA in toluene to effect lactonization, producing **44o** (Scheme 18).



Scheme 18. Formation of α-methylene lactones.

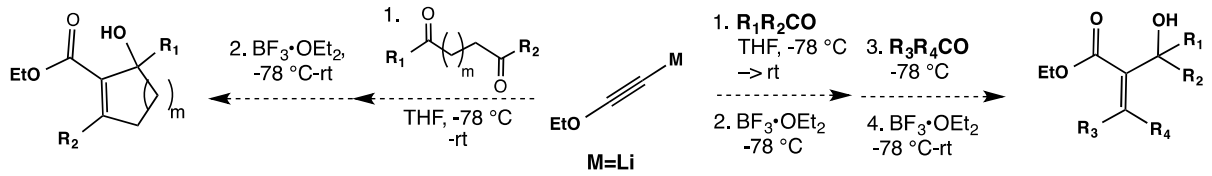
From a mechanistic standpoint, combination of metalated ynol ether (**40•Li**) with **41a** and BF_3•OEt_2 gives rise to intermediate **42a•BF_3Li**, which then participates in metathesis with the added equivalent of carbonyl compound activated by a second equivalent of BF_3•OEt_2 (Scheme 19). The *E/Z* mixture initially produced at the acyclic unsaturated ester stage then undergoes alkene *E*- to *Z*-isomerization and lactonization reactions facilitated by BF_3•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 due to a slower lactonization process, allowing complete alkene *E*-to-*Z* isomerization of the acyclic enoate to take place under the acidic reaction conditions.



Scheme 19. Mechanistic hypothesis for the Lewis acid-promoted tandem reaction.

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).



Scheme 20. Synthesis of Baylis-Hillman adducts by ynol ether-carbonyl tandem reactions.

6. 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, alkoxy cycloalkene carboxylate) and acyclic (γ,δ-unsaturated carboxylate) products 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 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.

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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.

ACKNOWLEDGMENT

This Account is dedicated to Professor Peter B. Dervan on the occasion of his 70th birthday. T.G.M. acknowledges the many contributions of students Aaron Christopher, Stephen Kelly, Dahniel Brandes, Juan Sosa, Vincent Tran, Kevin Ng and Armen Tudjarian to the research described herein on 1-alkynyl ethers. T.G.M. also thanks Professor Dan Little (UCSB) for DFT calculations and Professor Roald Hoffmann (Cornell U) for insightful mechanistic discussions on the *n*-BuLi-induced rearrangement of allyl-1,1-dichlorovinyl ethers. We also gratefully acknowledge the National Institutes of Health (SC3 GM 096899-01), the National Science Foundation (CHE-1508070), and the donors of the American Chemical Society Petroleum Research Fund (53693-URI) for their generous support of this research.

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