Graphical Abstract

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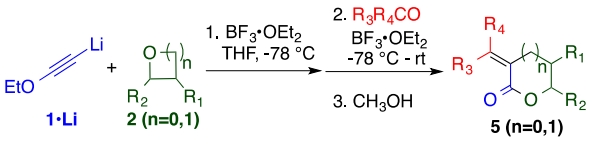

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A Single-Flask Synthesis of α-Alkylidene and α-Benzylidene Lactones from Ethoxyacetylene, Epoxides/Oxetanes, and Carbonyl Compounds

Kevin Ng,[a] Vincent Tran,[a] Thomas Minehan[a]*

[a]*Department of Chemistry and Biochemistry, California State University, Northridge, 18111 Nordhoff Street, Northridge, CA 91330, USA*

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ABSTRACT

Low temperature treatment of (ethoxyethynyl)lithium with epoxides or oxetanes in the presence of BF_3•OEt_2, followed by addition of aldehydes or ketones and warming to room temperature, affords structurally diverse five- and six-membered α-alkylidene and α-benzylidene lactones (**5**) in good to excellent yields. This one-pot process, in which three new carbon-carbon bonds and a ring are formed, affords substituted α,β–unsaturated lactones of predominantly *Z*-configuration. The reaction likely occurs *via* alkyne-carbonyl metathesis of a hydroxy-ynol ether intermediate, acid-promoted alkene *E*- to *Z*- isomerization, and lactonization.

The α-alkylidene lactone moiety is found in numerous synthetically challenging and biologically important natural products, many of which possess anticancer, antimalarial, antibacterial, antifungal, antiviral, and/or anti-inflammatory activities.[1] Of particular significance are the numerous members of the α-methylene-γ-butyrolactone family of sesquiterpenes, to which belong the germacranolides, (pseudo)guaianolides, eudesmanolides, and the cembranolides.[2] Recently, synthetic attention has also been directed toward the α-benzylidene-γ-butyrolactones megacerotonic acid and shimobashiric acid, due to their heightened biological profile.[3]

The α–alkylidene lactone motif is typically constructed by the condensation of lactone enolates with aldehydes or iminium ions,[4] by transition-metal mediated lactonizations,[5] or by Wittig or Horner-Wadsworth-Emmons-type reactions[6] between phosphorous ylides/phosphonate anions and carbonyl compounds.[1b] In the present Letter we describe a useful one-pot assembly α–alkylidene and α–benzylidene lactones from ethoxyacetylene, epoxides/oxetanes, and aldehydes or ketones.

Electron-rich alkynes, such as ynamines and ynol ethers, are functional groups that possess significant potential in organic chemistry for the formation of C-C bonds.[7] Due to their linear geometry, alkynyl ethers are relatively unhindered to approach by functional groups present in the same or different molecules; furthermore, alkynyl ethers can prospectively form up to three new bonds in a single reaction.[8] We have previously shown that *tert*-butyl ynol ethers bearing tethered alkenes form substituted cyclobutanones in high yields under mild thermal conditions (Figure 1).[8d] Furthermore, ynol ethers bearing pendant acetal groups undergo Lewis-acid catalyzed intramolecular cyclocondensation reactions to produce alkoxycycloalkene carboxylates.[8e]

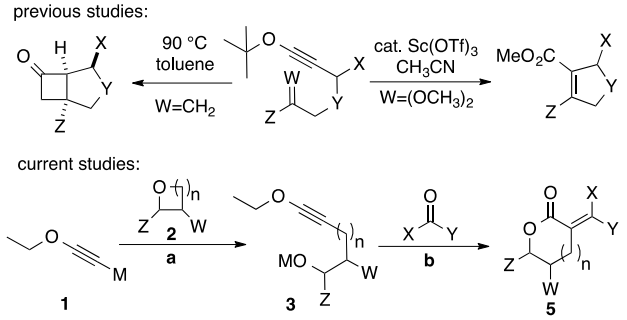


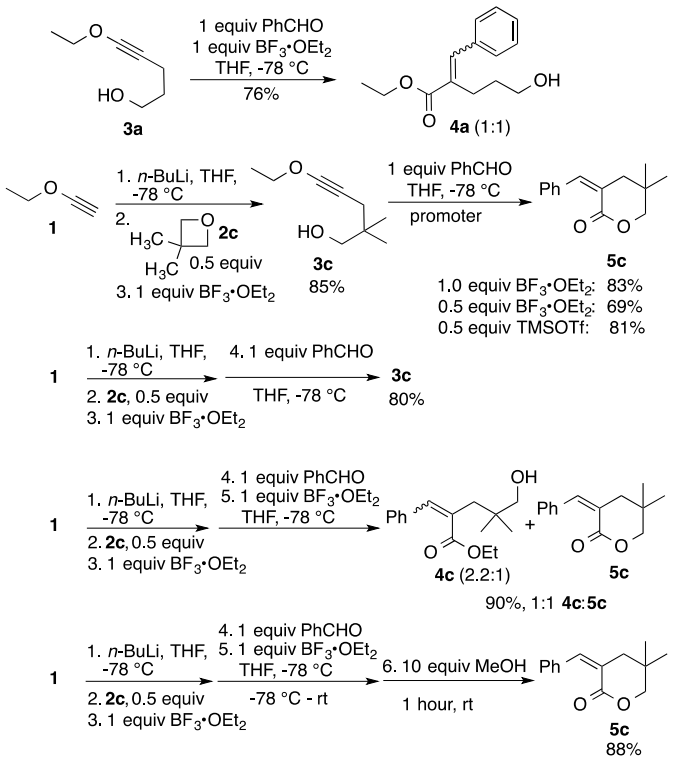
Figure 1. Previous and current studies.

While ynol ether-carbonyl metathesis reactions are well known,[7,8] we wished to explore the possibility of employing this reaction in the context of a tandem bond-forming process that would allow the rapid build up of molecular complexity in a single step. Specifically, we sought to combine the *intermolecular* electrophilic reaction of an ynol ether and a carbonyl compound with an *intramolecular* nucleophilic trap of the intermediate unsaturated ester, accomplishing the formation of two new carbon-carbon bonds and a ring (Figure 1, reaction b). In addition, the ynol ether substrate for this reaction (**3**, Figure 1) can be prepared by ring opening of cyclic ether **2** with metalated ethoxyacetylene (M=Li or BF_3Li, Figure 1, reaction a). Since Lewis acid is used to promote both of these reactions, the concept of combining these processes into a single transformation was

* Corresponding author. Tel.: +1-818-677-3315; fax: +1-818-677-4068; e-mail: thomas.minehan@csun.edu

appealing, and thus we sought conditions to accomplish the direct conversion of ynol ether **1** (M=H) to lactone **5**.

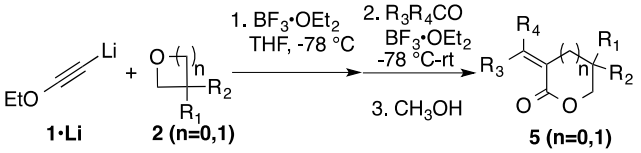
To explore the structural requirements for the tandem ynol ether-carbonyl condensation and lactonization transform (reaction b, Figure 1), we combined equimolar amounts of ynol ether **3a**, benzaldehyde, and BF_3•OEt_2 at -78 °C for 15 minutes (Scheme 1). Acyclic unsaturated ester **4a** was obtained in 76% yield as a ~1:1 *E:Z* stereoisomer mixture. Since no lactone was produced in this reaction, we reasoned that the gem-dimethyl (Thorpe-Ingold) effect[9] might facilitate the tandem processes of benzylidenation and lactonization. Thus, substrate **3c** was prepared (85% yield) by combining (ethoxyethynyl)lithium with 3,3-dimethyloxetane (0.5 equiv) and BF_3•OEt_2 (1.0 equiv) in THF at -78°C for two hours. After isolation, **3c** was condensed with benzaldehyde in THF at -78 °C in the presence of BF_3•OEt_2 (1.0 equiv) for fifteen minutes, giving rise to lactone **5c** in 83% yield. Substoichiometric amounts of BF_3•OEt_2 (0.5 equiv) or TMSOTf (0.5 equiv) in THF also promoted the efficient conversion of **3c** to **5c** (69% and 81%, respectively). Since BF_3•OEt_2 was shown to be an efficent promoter for both reactions in THF at -78 °C, we proceeded to combine (ethoxyethynyl)lithium, 3,3-dimethyl-oxetane (0.5 equiv), and BF_3•OEt_2 (1.0 equiv) in THF at -78°C for two hours, followed by addition of benzaldehyde (1.0 equiv). After 15 minutes of reaction at -78 °C, only ynol ether **3c** was evident in the reaction mixture; extending the reaction time or warming to room temperature did not effect conversion of **3c** to **5c**. Instead, addition of one equivalent of BF_3•OEt_2 at -78°C after addition of the benzaldehyde resulted in a clean conversion to an inseparable 1:1 mixture of acyclic unsaturated ester **4c** (as a 2.2:1 mixture of stereoisomers) and lactone **5c**. We reasoned that lactonization of **4c** could be facilitated by the presence of a Brønsted acid in the reaction medium, and thus after warming the mixture to room temperature, methanol (10 equiv) was added (promoting the formation of HF and/or fluoroboric acids) and the reaction was allowed to stir for one hour. An 88% isolated yield of lactone **5c** was obtained after column chromatography.

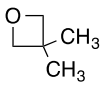
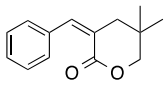
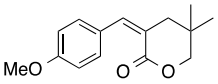
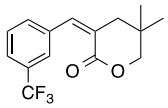
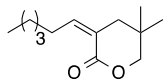
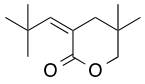
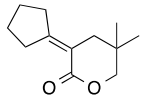
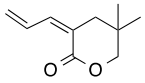
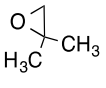
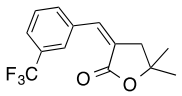
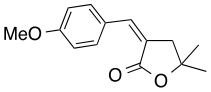
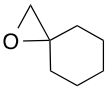
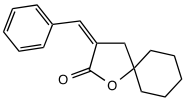


Scheme 1. Optimization of the **1→5** transformation.

Benzylidene lactone **5c** was obtained as a single isomeric alkene of *Z*-configuration (*vide infra*). Due to the excess amount of Lewis and Brønsted acids present in the reaction medium, it is possible that an initially formed *E*-alkene[15,16] or *E/Z* mixture[17] obtained after the ynol ether-carbonyl metathesis reaction (cf. **4a** and **4c**) underwent acid-promoted *E*- to *Z*- isomerization, a process likely driven by relief of $A^{1,3}$ strain in the *E* isomer (Scheme 4).[10]

Table 1. Scope of the one-pot synthesis of lactones **5** from **1**.[a]

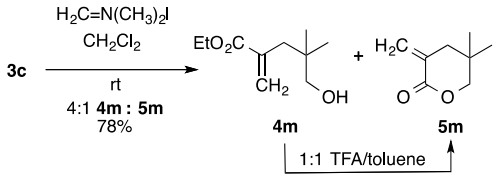


Entry	**2** (R_1=R_2)	R_3R_4CO	Product	Yield[b]
1	 **2c**	PhCHO	 **5c**	88
2	**2c**	4-OMe-C_6H_4CHO	 **5d**	65
3	**2c**	3-CF_3-C_6H_4CHO	 **5e**	79
4	**2c**	$CH_3(CH_2)_4$-CHO	 **5f**	55
5	**2c**	$(CH_3)_3C$-CHO	 **5g**	87
6	**2c**	$(CH_2)_4CO$	 **5h**	67
7	**2c**	CH_2=CH-CHO	 **5i**	92
8	 **2j**	3-CF_3-C_6H_4CHO	 **5j**	71
9	**2k**	4-OMe-C_6H_4CHO	 **5k**	69
10	 **2l**[11]	PhCHO	 **5l**	54

[a]Reaction conditions: **1** (1 mmol) in THF (0.25 M) was treated with *n*-BuLi (1 mmol) and stirred for 15 minutes. Then **2** (0.5 mmol) and BF_3•OEt_2 (1 mmol) were added and the mixture was stirred for 2 h. Then aldehyde or ketone (1 mmol) and BF_3•OEt_2 (1mmol) were added and the mixture was

allowed to warm to rt. Then MeOH (10 mmol) was added and the mixture was stirred for one hour. [b]Isolated yields after column chromatography.

As shown in Table 1, both electron-rich and electron-deficient aromatic aldehydes (entries 1-3, 8-10) are suitable carbonyl components for the tandem process, furnishing α-arylidene δ–valerolactones and γ–butyrolactones in very good overall yields. In addition, hindered and unhindered aliphatic aldehydes (entries 4 and 5) and cyclopentanone (entry 6) smoothly combined with **1** and **2** to furnish the corresponding α-alkylidenes **5f-5h**. Employing the α,β-unsaturated aldehyde acrolein in the reaction gave rise to a 92% yield of diene **5i** (entry 7), a potentially useful substrate for Diels-Alder reactions. Only two carbonyl substrate types proved problematic for this process: the aromatic ketone benzophenone and formaldehyde gave complex mixtures and low yields (<10%) in tandem reactions involving **1** and **2c**. Intriguingly, reaction of **3c** with Eschenmoser's salt[12] in CH_2Cl_2 at room temperature gave rise to a 1:4 mixture of α-methylene δ–valerolactone (**5m**) and acyclic enoate (**4m**), which upon exposure to 1:1 TFA/toluene at room temperature for 30 minutes resulted in a quantitative conversion to **5m** (Scheme 2).



Scheme 2. Formation of α-methylene lactone **5m**.

To extend this method to the synthesis of lactones without quaternary centers in the ring, we exposed (ethoxyethynyl)lithium to oxetane **2b** (0.5 equiv) and BF_3•OEt_2 (1.0 equiv) in THF at -78°C for two hours, followed by addition of benzaldehyde (1 equiv), BF_3•OEt_2 (1 equiv) and warming to room temperature. After stirring with methanol (10 equiv) for one hour or overnight, an inseparable ~2:1 mixture of acyclic unsaturated ester **4b** and lactone **5b** was obtained in 65% yield. When the reaction mixture was treated instead with 20 equiv of TFA for 4.5 hours, a 60% isolated yield of lactone **5b** was obtained after column chromatography (Scheme 3). It was subsequently found that TFA treatment was not necessary for the formation of γ-butyrolactones by this method; simply stirring the reaction mixture overnight at room temperature in the presence of 10 equiv of MeOH for the lactonization step gave the desired α–benzylidene and α–alkylidene products in good to excellent overall yields (Table 2).

Scheme 3. Formation of lactones lacking quaternary centers**.**

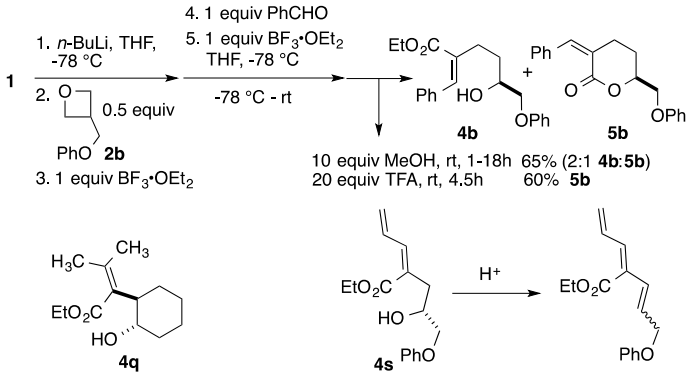
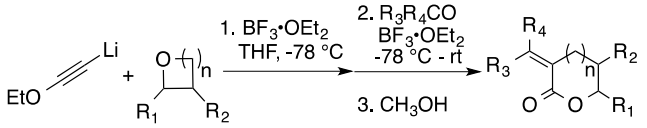
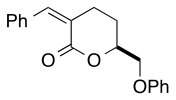
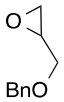
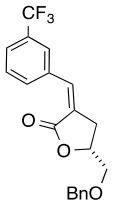
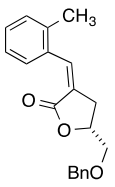
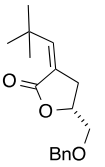
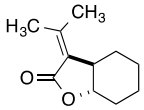
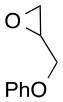
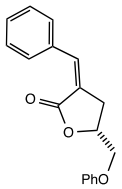
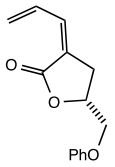


Table 2. Synthesis of lactones without ring quaternary centers.[a]



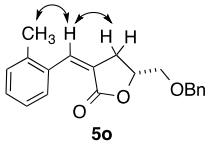
Entry	2	R_3R_4CO	Product	Yield[b]
1	 **2b**[13]	PhCHO	 **5b**	60[c]
2	 **2n**	3-CF_3-C_6H_4CHO	 **5n**	81
3	**2n**	2-CH_3-C_6H_4CHO	 **5o**	80[d]
4	**2m**	$(CH_3)_3C$-CHO	 **5p**	75
5	 **2q**	$(CH_3)_2CO$	 **5q**	62[e]
6	 **2r**	PhCHO	 **5r**	85
7	**2r**	CH_2=CH-CHO	 **5s**	50

[a] Reaction conditions: **1** (1 mmol) in THF (0.25 M) was treated with *n*-BuLi (1 mmol) and stirred for 15 minutes. Then **2** (0.5 mmol) and BF_3•OEt_2 (1 mmol) were added and the mixture was stirred for 2h. Then aldehyde or ketone (1 mmol) and BF_3•OEt_2 (1mmol) were added and the mixture was allowed to warm to rt. Then MeOH (10 mmol) was added and the mixture was stirred overnight. [b]Isolated yields after column chromatography. [c] TFA (20 equiv, 4.5 h, rt) was used instead of methanol for the lactonization step.

[d]Product formed as a 5:1 *Z:E* alkene isomer mixture. [e]The crude unsaturated ester was hydrolyzed (1N NaOH/MeOH) and then subjected to Yamaguchi/Yonemitsu conditions for lactonization with 2,4,6-trichlorobenzoyl chloride/Et_3N/DMAP in benzene for 12 h (see Supporting Materials).

As can be seen in Table 2, this protocol allows a range of sterically and electronically diverse α-arylidene (entries 2, 3, and 7) and α–alkylidene (entries 4 and 5) γ□butyrolactones to be prepared in good to excellent yields. Interestingly, the intermediate unsaturated ester **4q** derived from reaction of **1** with **2q** and acetone proved particularly sensitive to acid-promoted degradation during the prolonged stirring at room temperature required for the lactone-forming step. This difficulty could be circumvented by hydrolyzing crude **4q** (1:1 CH_3OH/1N NaOH, 15 minutes, rt; H_3O^+) to the corresponding seco acid and then stirring overnight in the presence of 2,4,6-trichlorobenzoyl chloride (under Yamaguchi/Yonemitsu lactonization conditions)[14] to furnish butyrolactone **5q** in 62% overall yield. Diene **5s** was prepared in moderate overall yield (50%) from **1**, **2r**, and acrolein due to the formation of side products derived from acid-mediated elimination of the alcohol in intermediate **4s** (Scheme 3).

The *Z*-stereochemistry of the alkene products was verified by ^{1}H-^{1}H NOESY experiments, in which crosspeaks were observed between the vinyl proton and the allylic methylene protons of the lactone. In the case of lactone **5o**, an additional cross-peak between the methyl group of the 2-tolyl substituent and the vinyl proton can be detected (Figure 2).

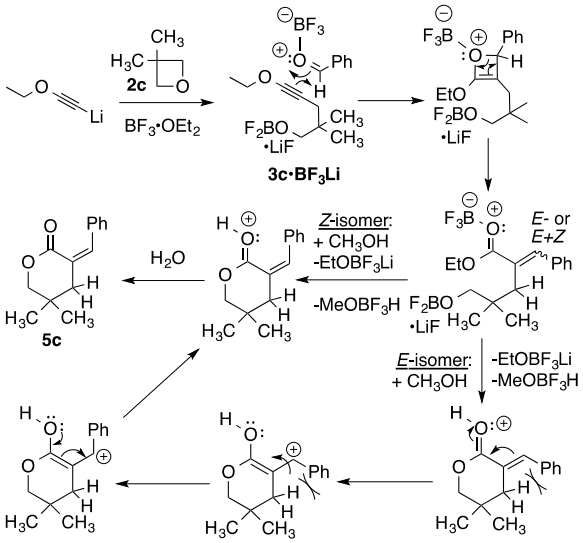


5o

Figure 2. Cross-peaks observed in the ^{1}H-^{1}H NOESY spectrum of **5o.**

Based on the observations reported in Schemes 1-3, a possible mechanism for this transformation (Scheme 4) involves the initial formation of ynol ether **3**•BF_3Li from **1** and **2** in the presence of BF_3•OEt_3, which then undergoes metathesis with an added carbonyl compound when it is activated by the second addition of BF_3•OEt_3. The acyclic unsaturated ester intermediate, which may initially be produced as the *E* isomer due to torquoselective ring opening of the oxetene intermediate,[15-17] is then engaged in alkene *E*- to *Z*-isomerization[10,17] and lactonization processes that are facilitated both by BF_3•OEt_2 and the Brønsted acid formed when methanol is introduced into the reaction medium. The olefin isomerization may take place either prior to[17] or after[10] lactonization; whereas **4c** is formed as a mixture of alkene isomers along with lactone **5c** (Scheme 1), intermediate **4b** (also isolated as an inseparable mixture with lactone **5b** after 18 h exposure to Brønsted acid after methanol addition) is of a single geometric configuration, suggesting that the *E*- to *Z*-interconversion process may take place before lactonization for some substrates.

In summary we have developed an efficient one-flask strategy for the synthesis of α-alkylidene and α-benzylidene lactones by the combination of ethoxyacetylene, epoxides/oxetanes, and carbonyl compounds. This operation achieves the formation of three new carbon-carbon bonds and ring, thus affording a significant increase in molecular complexity. The reaction also provides *Z*-configured unsaturated lactones stereoselectively, and likely proceeds through the intermediacy of an acyclic unsaturated ester that undergoes acid-promoted alkene *E*- to *Z*- isomerization and lactonization. We are currently exploring the utility of this process in natural product synthesis, and our results will be reported in due course.



Scheme 4. Proposed mechanism for formation of *Z*-alkylidene and benzylidene lactones.

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References and notes

1. (a) Elford, T. G.; Hall, D. G. *Synthesis* **2010**, 893. (b) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K *Angew. Chem. Int. Ed.* **2009**, *48*, 9426.
2. (a) Schall, A.; Reiser, O. *Eur. J. Org. Chem*. **2008**, 2353. (b) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 94. (c) Picman, A. K. *Biochem. Syst. Ecol*. **1986**, *14*, 255.
3. (a). Krabbe, S. W.; Johnson, J. S. *Org. Lett.* **2015**, *17*, 1188. (b) Brown, E.; Dhal, R.; Papin, N. *Tetrahedron* **1995**, *51*, 13061. (c) Papin, N.; Dhal, R.; Brown, E. *Nat. Prod. Lett.* **1994**, *4*, 303. (d) Takeda, R.; Hasegawa, J.; Shinozaki, M. *Tetrahedron Lett*. **1990**, *31*, 4159. (e) Takeda, R.; Hasegawa, J.; Shinozaki, M. *Proc. Phytochem. Soc. Eur*. **1990**, *29*, 201. (f) Murata, T.; Miyase, T.; Yoshizaki, F. *Chem. Pharm. Bull*. **2012**, *60*, 121.
4. (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl*. **1985**, *24*, 94. (b) Kalidindi, S.; Jeong, W. B.; Schall, A.; Bandichhor, R.; Nosse, B.; Reiser, O. *Angew. Chem. Int. Ed*. **2007**, *46*, 6361.
5. (a) Kummer, D. A., Brenneman, J. B.; Martin, S. F. *Org. Lett*. **2005**, *7*, 4621. (b) Lee, A. S.-Y.; Chang, Y.-T.; Wang, S.-H.; Chu, S.-F. *Tetrahedron Lett*. **2002**, *43*, 8489. (c) Sawant, M. S.; Katoch, R.; Trivedi, G. K.; Desai, U. R. *J. Chem. Soc. Perkin Trans. 1* **1998**, 843. (d) Kang, S.-K.; Kim, K.-J.; Hong, Y.-T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1584. (e) Yu, C.-M.; Hong, Y.-T.; Lee, J.-H *J. Org. Chem.*

2004, *69,* 8506. (f) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett*. **2005**, *7*, 593. (g) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Moro, L. *Eur. J. Org. Chem*. **1999**, 1137. (h) Ma, S.; Lu, X.; *J. Chem. Soc. Chem. Commun*. **1990**, 733. (i) Ma, S.; Lu, X. *J. Org. Chem*. **1991**, *56*, 5120. (j) Moise, J.; Arseniyadis, S.; Cossy, J. *Org. Lett*. **2007**, *9*, 1695. (k) Moise, J.; Sonawane, R. P.; Corsi, C.; Wendeborn, S. V.; Arseniyadis, S.; Cossy, J. *Synlett* **2008**, 2617. (l) Charruault, L.; Michelet, V.; Genfit, J.-P. *Tetrahedron Lett*. **2002**, *43*, 4757.

6. (a) Miyake, T.; Uda, K.; Kinoshita, M.; Fujii, M.; Akita, H. *Chem. Pharm. Bull*. **2008**, *56*, 398. (b) Edwards, M. G.; Kenworthy, M. N.; Kitson, R. R. A.; Scott, M. S.; Taylor, R. J. K. *Angew. Chem. Int. Ed*. **2008**, *47*, 1935. (c) Edwards, M. G.; Kenworthy, M. N.; Kitson, R. R. A.; Perry, A.; Scott, M. S.; Whitwood, A. C.; Taylor, R. J. K. *Eur. J. Org. Chem*. **2008**, 4769.
7. 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. For reviews on the synthetic utility of ynolates and silyl ynol ethers, see: (a) Shindo, M.; Matsumoto, K. *Top. Curr. Chem.* **2012**, *327*, 1. (b) Shindo, M. *Tetrahedron* **2007**, *63*, 10. (b) Shindo, M. *Chem. Soc. Rev.* **1998**, *27*, 367. (c) Shindo, M. *Synthesis*, **2003**, *15*, 2275. For reviews on the chemistry of ynamides, see: (a) Cook, A. M.; Wolf, C. *Tetrahedron Lett.* **2015**, *56*, 2377. (b) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B.L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47,* 560. (c) De Korver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem Rev.* **2010**, *110*, 5064. (d) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840.
8. (a) Zhao, W.; Li, Z.; Sun, J. *J. Am. Chem. Soc.* **2013**, 4680. (b) Zakarya, D.; Rayadh, A.; Samih, M.; Lakhlifi, T. *Tetrahedron Lett.* **1994**, *35*, 405. (c) Krashnaya, Z. A.;Levchenko, T. S.; Rudenko, B. A.; Kucherov, V. F. *Izv. Akad. Nauk SSR Ser. Khim.* **1965**, *2*, 313. (d) Tran, V.; Minehan, T. G. *Org. Lett.* **2011**, *13*, 6588. (e) Tran, V.; Minehan, T. G. *Org. Lett.* **2012**, *14*, 6100.
9. (a) Bachrach, S. M. *J. Org. Chem.* **2008**, *73*, 2466. (b) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080.
10. (a) Johnson, F. *Chem Rev.* **1968**, *4*, 375. (b) Ramachandran, P. V.; Garner, G.; Pratihar, D. *Org. Lett.* **2007**, *9*, 4753. Treatment of **3a** and benzaldehyde with substoichiometric amounts of BF_3OEt_2 (0.5 equiv) in CH_2Cl_2 or THF at -78 °C also produced **4a** as a 1:1 mixture of *E:Z* alkene stereosiomers. No conditions were found that produced the *E*- isomer predominantly or exclusively.
11. For the preparation of epoxide **2l**, see: Djigoue, G. B.; Kenmogne, L. C.; Roy, J.; Poirer, D. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6360.
12. Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 330.
13. For the preparation of oxetane **2b** see: Fitton, A.O.; Hill, J.; Jane, D.E.; Millar, R. *Synthesis* **1988**, *12*, 1140.
14. (a) Inanagana, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989. (b) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett*. **1990**, *31*, 6367. (c) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem*. **1990**, *55*, 7.
15. For theoretical work on the torquoselective 4e-electrocyclic ring opening of cyclobutenes, see: (a) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989. (b) Kallel, E. A.; Wang, Y.; Spellmeyer, D. C.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 6759. (c) Dolbier, W. R. Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471. (d) Lee, P. S.; Zhang, X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 5072.
16. For studies on *E/Z* selectivity of the reactions of ynolates with carbonyl compounds, see: (a) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840. (b) Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, *69*, 3912. (c) Mori, S.; Shindo, M. *Org. Lett.* **2004**, *6*, 3945.
17. Whereas *E*-acrylic amides are selectively formed in BF_3•OEt_2-mediated (0.5 equiv) reactions of ynamides and aldehydes at -78 °C, mixtures of *E*- and *Z*- alkene isomers are obtained when the analogous reaction is performed at 0 °C with unsymmetrical and sterically differentiated ketones: You, L.; Al-Rashid, Z. F.; Figueroa, R.; Ghosh, S. K.; Li, G.; Lu, T.; Hsung, R. P. *Synlett* **2007**, *11*, 1656.

Supplementary Material

Supplementary data (synthetic procedures, spectroscopic data and ^1H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at.