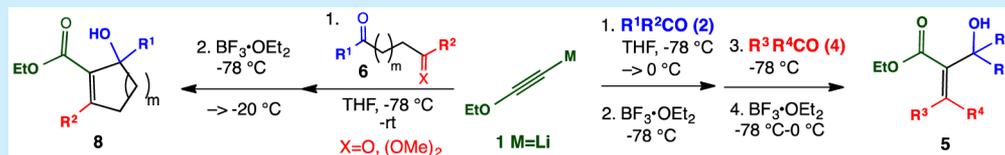


A Single-Flask Synthesis of Morita–Baylis–Hillman Adducts from Ethoxyacetylene and Carbonyl Compounds: Synthesis of Subamolides D and E

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S Supporting Information



ABSTRACT: Sequential treatment of (ethoxyethynyl)lithium with aldehydes and/or ketones (2 and 4) and $\text{BF}_3 \cdot \text{OEt}_2$ gives rise to β -hydroxyenoates 5 in good to excellent overall yields. Similarly, the combination of 1 ($\text{M} = \text{Li}$) and dicarbonyl compounds 6 ($\text{X} = \text{O}$) or keto/aldehyde acetals ($\text{X} = \text{OMe}$) followed by the addition of a Lewis acid leads to five-, six-, and seven-membered hydroxycycloalkene carboxylates. The utility of this method is demonstrated in the synthesis of the α -alkylidene lactone natural products subamolide D and E.

The Morita–Baylis–Hillman (MBH) reaction, which involves the coupling of activated alkenes or alkynes and electrophiles under Lewis base catalysis, is a versatile reaction in organic synthesis for the formation of carbon–carbon bonds.¹ The intramolecular variant of this process, in which the activated alkene and electrophile components are present in the same molecule, allows the preparation of diverse carbocyclic and heterocyclic systems.² In addition to tertiary amines and alkyl (aryl) phosphines, both Bronsted and Lewis acids have been demonstrated to be efficient promoters for this process, and asymmetric reactions employing chiral catalysts allow the synthesis of optically active products.³ Since Morita–Baylis–Hillman adducts are densely functionalized molecules, they are highly useful as intermediates in the synthesis of interesting natural and designed products of medicinal import.^{4–7} In view of the importance of MBH adducts in organic synthesis, the development of new methods for their efficient preparation is of great importance. In the present Letter, we describe a useful condensation of ynol ethers and carbonyl compounds in the presence of Lewis acids that affords cyclic and acyclic Morita–Baylis–Hillman adducts in a one-pot reaction.

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.⁸ We have previously shown that five- and six-membered *Z*- α -alkylidene- and *Z*- α -benzylidene lactones can be prepared efficiently in a single flask from the reaction of metalated ethoxyacetylene, epoxides or oxetanes, and aldehydes or ketones in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ as a promoter (Figure 1).⁹ Three new carbon–carbon bonds and a ring are created in the process, with a significant increase in molecular complexity realized in a rapid

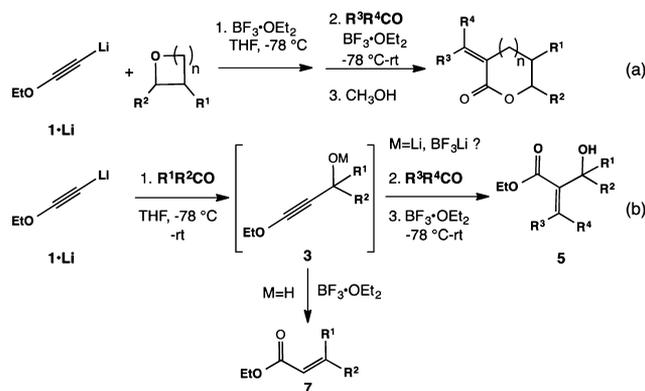


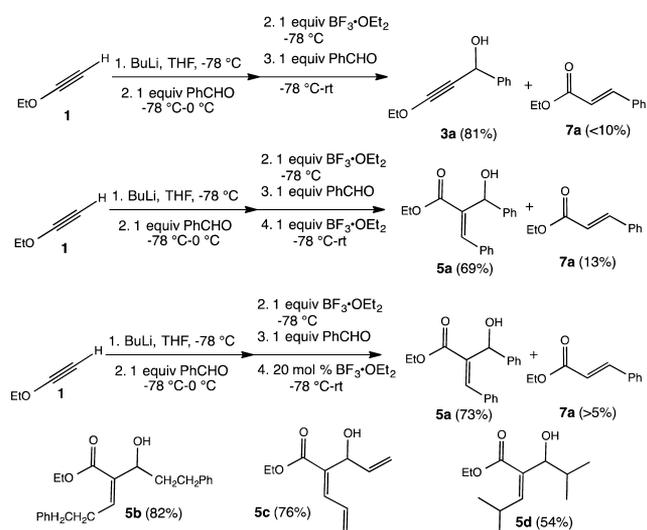
Figure 1. Previous (a) and current (b) single-flask transformations of metalated ynol ether 1.

fashion. We wished to extend this process to the preparation of MBH adducts by sequentially combining metalated ethoxyacetylene and two carbonyl compounds in the presence of a Lewis acid; however, a potential side reaction which could complicate this process is the facile Meyer–Schuster rearrangement of intermediate 3, which has been extensively utilized for the synthesis of α,β -unsaturated esters of the type 7 from metalated ynol ethers and aldehydes and ketones.¹⁰

We initiated our studies by combining (ethoxyethynyl)lithium (2.1 mmol) with benzaldehyde (1.4 mmol) at -78°C in THF (Scheme 1); after a brief warming to 0°C (10 min), complete consumption of benzaldehyde was observed by thin

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Scheme 1. Reaction of Ynol Ethers **1** with Aldehydes in the Presence of $\text{BF}_3 \cdot \text{OEt}_2$ 

layer chromatography. After recooling to $-78\text{ }^\circ\text{C}$, the lithium alkoxide intermediate was treated with $\text{BF}_3 \cdot \text{OEt}_2$ (2.1 mmol), followed by addition of a second equivalent of benzaldehyde (1.4 mmol). TLC showed no conversion of the initial aldehyde adduct, and the mixture was allowed to warm to $0\text{ }^\circ\text{C}$ and stir for 30 min. An 81% yield of alcohol **3a** was isolated after column chromatography; less than 10% of ethyl cinnamate **7a** was also produced. This result indicated that the lithium alkoxide– $\text{BF}_3 \cdot \text{OEt}_2$ complex did not significantly undergo a Meyer–Schuster reaction between -78 and $0\text{ }^\circ\text{C}$. The experiment was then repeated, and the lithium alkoxide intermediate was combined with $\text{BF}_3 \cdot \text{OEt}_2$ (2.1 mmol), benzaldehyde (2.1 mmol), and an additional equivalent of $\text{BF}_3 \cdot \text{OEt}_2$ (2.1 mmol) at $-78\text{ }^\circ\text{C}$ in THF. Upon warming to $0\text{ }^\circ\text{C}$, MBH adduct **5a** was produced in 69% yield, along with 13% of **7a**. It was found that the amount of cinnamate produced could be decreased by lowering the amount of the second addition of $\text{BF}_3 \cdot \text{OEt}_2$ to 20 mol % (0.42 mmol). In this manner, a 73% isolated yield of **5a** could be secured, with less than 5% of **7a** produced in the reaction mixture.

Applying this protocol to dihydrocinnamaldehyde, acrolein, and isobutyraldehyde gave adducts **5b–5d** in 54–82% isolated yields, respectively. Although the second addition of a full equivalent (2.1 mmol) of $\text{BF}_3 \cdot \text{OEt}_2$ was required for optimal yields of products **5b** and **5d**, the corresponding Meyer–Schuster products **7b** and **7d** were formed in only trace quantities (>5%), indicating that the acid-promoted rearrangement process is less favored for alkoxide intermediates derived from addition of (ethoxyethynyl)lithium to aliphatic aldehydes. It is interesting to note that while **5a** and **5c**, both derived from unsaturated aldehydes, are produced as the *E*-alkene stereoisomer predominantly (as verified by NOESY experiments, see Supporting Information, and comparison of ^1H NMR spectra with literature data¹⁸), the predominant isomer of compounds **5b** and **5d** is of the *Z* configuration. Whereas the *E* isomer of **5a** and **5c** may be favored by π – π type interactions, A – $1,3$ strain present in the *E* isomers of **5d** and **5d** may favor acid-promoted *E*-to-*Z* isomerization, as has been previously shown for both cyclic and acyclic enoates.⁹

Table 1 shows the extension of this method to the preparation of Morita–Baylis–Hilman adducts from two different carbonyl components.

Table 1. Scope of Reaction of **1** with Aldehydes and Ketones

entry	2	4	5	yield (5) ^b
1	$(\text{CH}_3)_3\text{CCHO}$	PhCHO		91
2	$(\text{CH}_3)_3\text{CCHO}$	PhCH ₂ CH ₂ -CHO		84
3	3-CF ₃ -C ₆ H ₄ CHO	CH ₃ (CH ₂) ₈ -CHO		73
4		PhCH ₂ CH ₂ -CHO		58
5	2-CH ₃ -C ₆ H ₄ CHO	CH ₂ CH-CHO		79 ^c
6	$(\text{CH}_3)_2\text{CO}$	4-OCH ₃ -C ₆ H ₄ CHO		68
7		CH ₂ CH-CHO		81

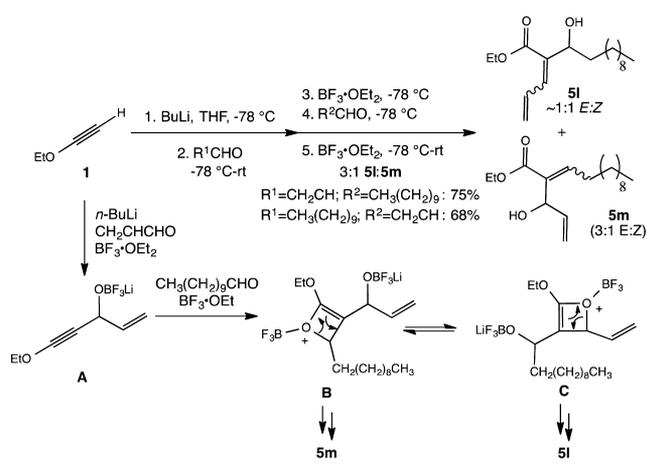
^aAll reactions were carried out using ethoxyacetylene (2.1 mmol) in THF (1 M), *n*-BuLi (2.1 mmol), **2** (1.4 mmol), $\text{BF}_3 \cdot \text{OEt}_2$ (2.1 mmol), **4** (2.1 mmol), and $\text{BF}_3 \cdot \text{OEt}_2$ (2.1 mmol). ^bIsolated yields after column chromatography. ^cIsolated as a 5:1 *E/Z* mixture of alkene isomers.

A variety of hindered and unhindered aliphatic (entries 1–4), aromatic (electron-deficient, sterically encumbered, and electron-rich entries 3, 5, and 6), and α,β -unsaturated (entries 5 and 7) aldehydes and both cyclic and acyclic ketones (entries 4, 6, and 7) participate in this process as either the first (**2**) or second (**4**) carbonyl component. The *Z*-alkene geometry predominates in all cases except when both **2** and **4** are unsaturated carbonyl compounds (entry 5). Intriguingly, the sequential combination of (ethoxyethynyl) lithium, cyclo-

pentanone (carbonyl component 1), and dihydro-cinnamaldehyde (carbonyl component 2, entry 4) according to the above-described protocol gave the *rearranged* β -hydroxy enoate **5h** exclusively. Reversing the order of carbonyl addition also gave **5h**, albeit in lower overall yield (35%), implying a Lewis acid mediated equilibrium process favoring the formation of the more stable tetrasubstituted enoate product (see below).

We were interested in preparing adducts of the type **5m** (Scheme 2) as advanced precursors for the synthesis of α -

Scheme 2. Formation of Product Mixtures with Acrolein and Undecanal

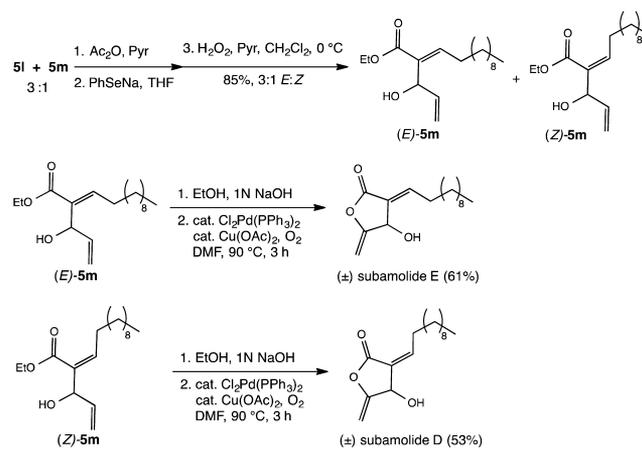


alkylidene lactone natural products. However, exposure of (ethoxyethynyl)lithium to acrolein, followed by successive treatment with $BF_3 \cdot OEt_2$, undecanal, and $BF_3 \cdot OEt_2$, gave rise to a 1:3 mixture of alcohol **5m** and rearranged alcohol **5l** in 75% yield. Quenching the reaction at lower temperatures ($-40^\circ C$, $-10^\circ C$) did not increase the proportion of **5m** formed, and lowering the amount of Lewis acid added in the second step (50 mol %, 20 mol %) decreased the overall yields of adducts obtained without significantly effecting the **5l**:**5m** ratio. Again, reversing the order of aldehyde addition led to the same ratio of products **5l** and **5m** in 68% yield. It is likely that the combination of ynolether intermediate **A** with undecanal and $BF_3 \cdot OEt_2$ gives rise to oxonium ion **B**, in equilibrium with oxonium ion **C**, which produce **5m** and **5l**, respectively, upon ring opening. The predominance of **5l** may be due to the greater stability of the conjugated diene unit relative to the isolated diene of **5m**.

It was nonetheless possible to transform the mixture of **5l** and **5m** into **5m** exclusively in high yield (85%) by a sequence involving acylation (Ac_2O , Pyr), allylic substitution with sodium phenylselenide ($NaSePh$, THF, rt, 10 min),¹¹ and oxidation (H_2O_2 , pyr, CH_2Cl_2 , $0^\circ C$, 20 min).¹² This protocol conveniently provides a separable 3:1 mixture of *E* and *Z* enoates **5m** (Scheme 3).

Subamolides D and E are two naturally occurring α -alkylidene lactones which have been shown to be DNA damaging agents capable of inducing apoptosis in malignant cells (Scheme 3).¹³ Hydrolysis of the ethyl ester of (*E*)-**5m** and oxidative cyclization of the unsaturated acid with catalytic quantities of $Cl_2Pd(PPh_3)_2$ and $Cu(OAc)_2$ under an atmosphere of oxygen¹⁴ directly afforded racemic subamolide E in 61% overall yield; an analogous treatment of (*Z*)-**5m** gave (\pm)-subamolide D in 53% overall yield. To date this appears to

Scheme 3. Synthesis of (\pm)-Subamolides E and D



be the shortest synthetic pathway to this class of natural products.¹⁵

Next, we wished to explore the possibility of forming cyclic MBH adducts through the use of dicarbonyl compounds as reaction partners. Indeed, the combination of (ethoxyethynyl)lithium (1.5 equiv) with phthalic dicarboxyaldehyde (1.0 equiv) in THF at $-78^\circ C$, followed by warming to $0^\circ C$ for 10 min, recoiling to $-78^\circ C$, and treatment with $BF_3 \cdot OEt_2$ (2.4 equiv), gave rise to hydroxycyclopentene carboxylate **8a** in 71% isolated yield after warming to $-20^\circ C$ for 15 min (Table 2, entry 1). Employing acetonyl acetone (Table 2, entry 2) as the dicarbonyl compound gave the desired tertiary alcohol **8b** in 62% yield upon quenching the reaction mixture at $-20^\circ C$; if the mixture was instead allowed to warm to room temperature, cyclopentadiene **8b'** (see Supporting Information) was the major product, likely arising from Lewis acid mediated elimination of the tertiary alcohol. To circumvent the elimination process at elevated temperatures, we investigated the use of keto-acetal and aldehyde-acetal substrates instead of dicarbonyl compounds, since we have previously shown that intramolecular condensation of ynolether acetals takes place rapidly at room temperature in the presence of Lewis acids to form alkoxy-cycloalkene carboxylates.¹⁶ Indeed, exposure of (ethoxyethynyl)lithium to aldehyde-acetals (**6c**–**6e**, **6g**, entries 3–5, 7) or keto acetal (**6f**, entry 6) in THF from $-78^\circ C$ to rt, followed by addition of $BF_3 \cdot OEt_2$ at $-78^\circ C$ and warming to room temperature, gave the corresponding five-, six-, and seven-membered hydroxycycloalkene carboxylates **8c**–**8g** in good to excellent yields (Table 2) with no evidence of diene formation.

In summary we have developed an efficient and direct method for the synthesis of cyclic and acyclic Morita–Baylis–Hillman adducts from ethoxyacetylene and carbonyl compounds. This one-pot process results in the formation of three new carbon–carbon bonds, and the products are richly functionalized to allow further bond formations via conjugate addition or allylic substitution reactions.¹⁷ The utility of this process has been demonstrated in the synthesis of subamolides D and E. We are continuing to explore the applications of this method in natural product synthesis.

Table 2. Scope of Reaction of 1 with Carbonyl Compounds 6^a

entry	6	8	yield (8) ^b
1			71 ^c
2			62 ^c
3			68
4			82
5			74
6			91
7			93

^aAll reactions were carried out using ethoxyacetylene (2.1 mmol) in THF (1 M), *n*-BuLi (2.1 mmol), 6 (1.4 mmol), and BF₃·OEt₂ (3.4 mmol). ^bIsolated yields after column chromatography. ^cThe reaction mixture was quenched at -20 °C instead of rt.

NMR spectra of new compounds in Tables 1 and 2 and Schemes 1–3 (PDF)

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Notes

The authors declare no competing financial interest.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01772.

Experimental procedures, spectroscopic and analytical data (PDF)