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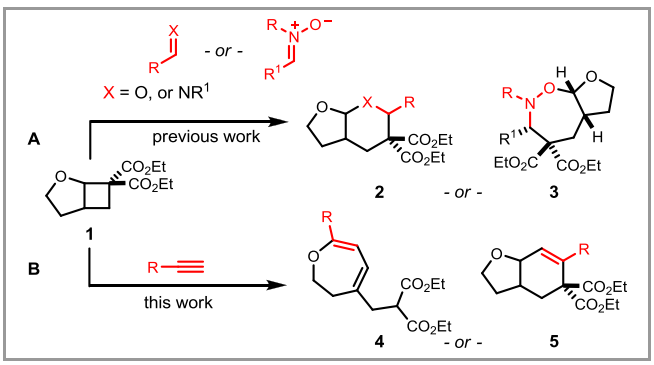
Abstract: In the presence of BF_3·OEt_2 cyclobutane-1,1-diesters undergo a reaction with terminal alkynes to quickly access dihydrooxepines.

Key words: donor-acceptor cyclobutanes, oxepine, alkynes, Lewis acid, [4+2] cycloaddition

Reactions of strained ring systems are becoming increasingly prominent for the creation of complex molecules.[1] Donor-acceptor (DA) cyclopropanes have been shown to be suitable building blocks for rapidly increasingly molecular complexity through rearrangement and cycloaddition reactions,[1] and they have been deployed in the total synthesis of natural products.[2] DA cyclobutanes have recently garnered a great deal of attention, as cycloadditions with these species can provide access to larger ring systems than those derived from their smaller cyclopropane counterparts. Although DA cyclobutanes have been shown to provide facile access to highly substituted heterocycles, their chemistry has been comparatively less thoroughly explored.[3]

We have recently reported the Lewis acid-catalyzed formal [4+2] cycloadditions of alkoxy substituted DA-cyclobutanes with several heteroatom-containing dipolarophiles, including imines,[4a] aldehydes,[4b] and nitrones (Scheme 1A).[4c] While there has been much success in forming heterocyclic compounds through formal dipolar cycloadditions with cyclobutanes,[5] there has been few studies detailing their reactivity with all-carbon dipolarophiles.[6]



Scheme 1 Previous and current studies with cyclobutane-1,1-diesters and various dipolarophiles

Herein, we report the first Lewis acid-catalyzed reactions of terminal alkynes with DA-cyclobutanes (Scheme 1B). Instead of undergoing the anticipated formal [4+2] cycloaddition to give **5**, these compounds underwent an unusual addition-rearrangement sequence to generate 2,3-dihydrooxepines **4**. This reaction may prove useful for accessing the 7-membered oxacyclic core found in various of natural products (Figure 1).[7]

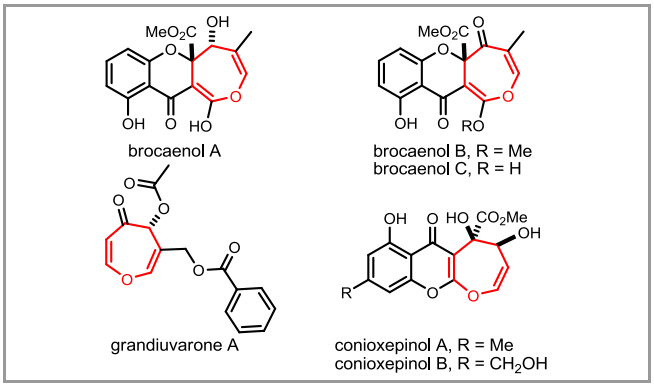


Figure 1 Selected examples of 7-membered oxacyclic natural products

Initial investigations began by treating DA cyclobutane **1** with phenylacetylene. A thorough screening of many Lewis acids under an array of temperatures, solvents and pressures resulted only in extensive substrate decomposition.[8] Treatment with BF_3·OEt_2, however, afforded a new compound whose spectrum was consistent with dihydrooxepine scaffold **4** (Figure 2).

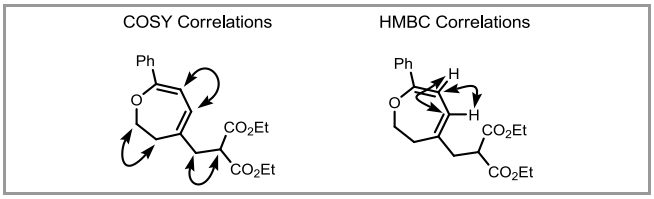


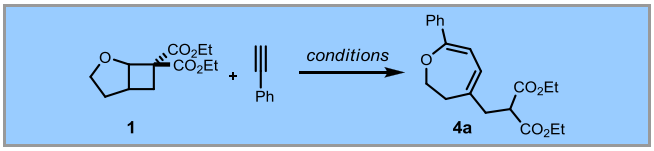
Figure 2 2-D NMR correlations which were used to determine the structure of the reaction product

Further studies to optimize the formation of the dihydrooxepine (**4a**) using BF_3·OEt_2 as the Lewis acid were undertaken, and the results are summarized in Table 1. Cyclobutane **1** and phenylacetylene were chosen for optimization due to their high stability and ease of access. Though a variety of solvents allowed

for the formation of the desired product, 1,2-dichloroethane (DCE) gave the highest yields.

At ambient temperatures the reaction was very slow, requiring 18 hours for consumption of the cyclobutane starting material. Treating the cyclobutane in the absence of alkyne confirmed slow decomposition was occurring, and it was found that better yields were obtained at 84 °C (compare entries 1,2 and 7 with 3,4, and 6). Although, the reaction proceeded to completion with catalytic $BF_3{\cdot}OEt_2$, a stoichiometric amount of the reagent was used as the resulting reaction mixtures were cleaner by ^1H NMR analysis (Table 1, entries 4 and 6). The fully optimized conditions involved the use of 1 equivalent of $BF_3{\cdot}OEt_2$ in refluxing DCE (Table 1, entry 6).

Table 1 Effect of $BF_3{\cdot}OEt_2$ loading, solvent and temperature

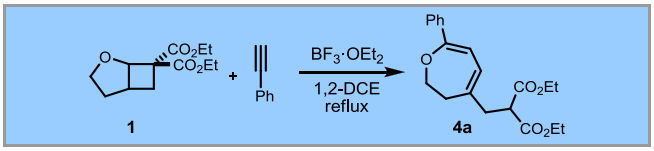


Entry[a]	$BF_3{\cdot}OEt_2$ Loading	Solvent[b]	Time	Temperature	Yield (%)
1	10 mol %	DCE	18 h	r.t.	27
2	10 mol %	DCE	30 min	40 °C	28
3	10 mol %	DCE	30 min	reflux	33
4	10 mol %	DCE	15 min	reflux	35
5	10 mol %	$CHCl_3$	30 min	reflux	24
6	**1 equiv**	**DCE**	**15 min**	**reflux**	**41**
7	1 equiv	DCE	1 h	r.t.	20
8	1 equiv	PhMe	15 min	reflux	38
9	1 equiv	benzene	15 min	reflux	26
10	1 equiv	$MeNO_2$	15 min	reflux	16
11[c]	1 equiv	DCE	1 min	80 °C	34

(*a*) Typical reaction conditions: 0.4 mmol of **1**, 1.1 equiv of phenylacetylene, solvent (3mL). (*b*) DCE = 1,2-dichloroethane, PhMe = toluene, $MeNO_2$ = nitromethane. (*c*) Reaction performed in a microwave reactor.

Reaction concentration also significantly affected the reaction, and the optimal concentration was found to be 0.06 M of cyclobutane **1** (Table 2).

Table 2 Effect of concentration of **1** on formation of **3**

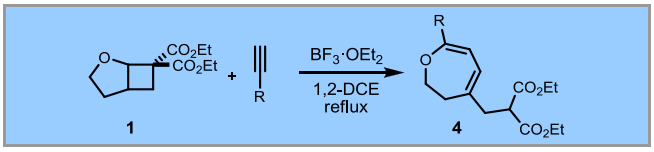


Entry[a]	Concentration of **1**[M]	Yield (%)[b]
1	0.1	41
2	**0.06**	**53**
3	0.05	51
4	0.03	49
5	0.02	43

(*a*) All reactions were complete in approximately 15 minutes. Each reaction was run with 0.4 mmol of cyclobutane **1** and 1.1 equiv of alkyne. (*b*) Average of two or more runs.

With adequate reaction conditions having been identified, the scope of the reaction was investigated with various terminal alkynes (Table 3). In general, electronically neutral aryl acetylenes were the most compatible substrates (Table 3, entries 1-6). These include aliphatic substitution (entry 2), as well as bromo- and iodo-containing substrates (entries 3 and 4). Moderately electron rich aryl groups were compatible (entry 6), but more electron rich alkynes rapidly polymerized upon exposure to $BF_3{\cdot}OEt_2$ (entry 7). Electron poor alkynes failed to react with the cyclobutane which slowly decomposed, whereas the alkyne could be quantitative recovered (Table 3, entry 8), Sterically bulky alkynes such as 9-ethylanthracene led to decomposition of cyclobutane **1** and recovery of the alkyne (Table 3, entry 9). Additionally, heteroatom substituted alkynes and aliphatic alkynes resulted in decomposition of the both the cyclobutane and alkyne (entries 10 - 12).[9]

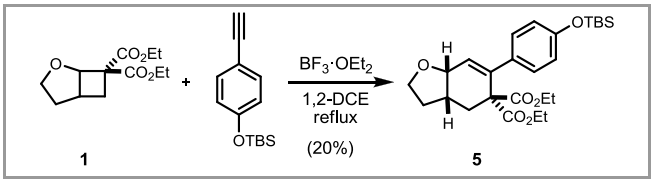
Table 3 Scope of the $BF_3{\cdot}OEt_2$ reaction of cyclobutane **1** and terminal alkynes



Entry[a]	R	Product	Yield (%)
1	Ph	**4a**	53
2	4-Me-C_6H_4	**4b**	34
3	4-Br-C_6H_4	**4c**	31
4	4-I-C_6H_4	**4d**	36
5	1-napthyl	**4e**	35
6	4-OAc-C_6H_4	**4f**	35
7	4-OMe-C_6H_4	-	0[b]
8	4-NO_2-C_6H_4	-	0[b]
9	9-anthracenyl	-	0[c]
10	*N*-tosyl-3-indolyl	-	0[d]
11	*N*-methyl-3-indolyl	-	0[d]
12	*n*-Bu	-	0[d]

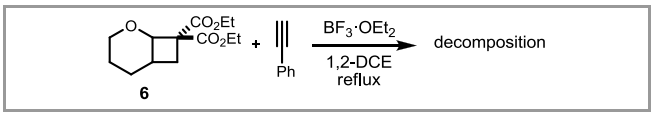
(*a*) Typical reaction conditions: 0.4 mmol of **1**, 1.1 equiv of alkyne, 1 equiv of $BF_3{\cdot}OEt_2$, 1,2-DCE (6 mL), immersed in a pre-heated oil bath. (*b*) **1** decomposed, alkyne decomposed. (*c*) **1** decomposed, 71 % of alkyne recovered. (*d*) **1** decomposed, >90 % of alkyne recovered.

While moderate results were obtained with *para*-acetoxy phenylacetylene (*vide supra*), we were surprised to discover that when a silyl ether was employed, the product obtained was cyclohexene **5**, the result of a formal cycloaddition rather than the addition-rearrangement product observed thus far (Scheme 2). This example was the first and only instance where the bicyclic cycloadduct **5** was observed and not the oxepine product **4**.



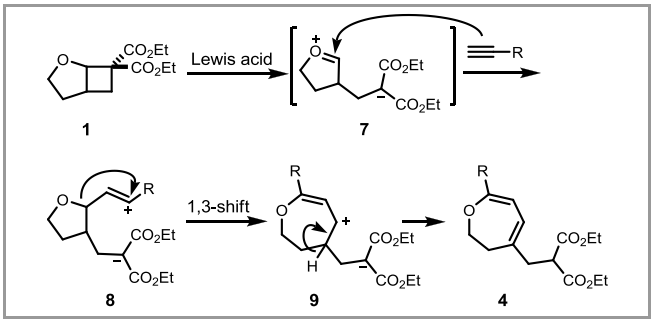
Scheme 2 Reaction of a silyl ether substituted ethynyl benzene with cyclobutane **1**

The reactivity of additional cyclobutanes such as the pyran-substituted cyclobutane **6** was examined with phenyl acetylene under the standard reaction conditions, but only decomposition occurred and neither the rearrangement product nor the cycloadduct were observed (Scheme 3).



Scheme 3 Reaction of a pyran-substituted cyclobutane with phenylacetylene

A proposed mechanism is presented in Scheme 4. The Lewis acid activation of diester **1** likely results in cleavage of the strained carbon-carbon bond between donor and acceptor moieties to generate a zwitterionic intermediate **7**. The terminal alkyne can then attack at the carbon atom of the oxocarbenium to provide transient carbocation **8**, which undergoes a 1,3-shift to the more stable allylic carbocation **9**. Upon proton loss, the final oxepine product **4** would be obtained.



Scheme 4 Proposed mechanism for the formation of oxepine **3** from cyclobutane **1**

This letter reports the first reaction of DA-cyclobutanes with terminal alkynes in the presence of a Lewis acid. These oxepines are formed through an intriguing addition-rearrangement sequence. This methodology is currently being investigated for potential application towards the formation of fully saturated oxepines and the total synthesis of natural products.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals-/toc/synlett.

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(8) Lewis acids screened included: $Yb(OTf)_3$, $Sc(OTf)_3$, $Zn(OTf)_2$, $ZnBr_2$, $MgCl_2$, $MgBr_2$, $InBr_3$, $TiCl_4$, $Cu(OTf)_2$, $BiCl_3$ at temperatures ranging from 0 °C to refluxing and at ambient pressure to 160000 psi in a high pressure reactor.

(9) **Representative procedure for the preparation of 4a:** To a solution of cyclobutane **1** (105 mg, 0.43 mmol, 1 equiv) and phenylacetylene (50 µL, 0.49 mmol, 1.1 equiv) in 1,2-dichloroethane (6 mL, 0.1 M) was added $BF_3{\cdot}OEt_2$ (55 µL, 0.43 mmol, 1 equiv). A reflux condenser was quickly attached and the flask was placed in a pre-heated oil bath. After complete consumption of the cyclobutane as indicated by TLC (15 min), the reaction mixture was poured into a separatory funnel containing a half saturated solution of $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered through a pad of celite and concentrated *in vacuo*. The crude reaction product was purified by flash column chromatography (4:1 hexanes/EtOAc) to provide the corresponding addition-rearrangement product **4a** (79 mg, 53 %) as a yellow oil. R_f 0.49 (4:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 – 7.55 (m, 2H), 7.31 – 7.29 (m, 2H), 7.27 – 7.25 (m, 1H), 5.72 (d, *J* = 8.8 Hz, 1H), 5.53 (d, *J* = 8.8 Hz, 1H), 4.32 (app t, *J* = 4.1 Hz, 2H), 4.19 (q, *J* = 4.0 Hz, 4H), 3.55 (t, *J* = 7.9 Hz, 1H), 2.73 (d, *J* = 8.2 Hz, 2H), 2.62 (app t, *J* = 4.1 Hz, 2H), 1.25 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0 (2), 157.4, 137.5, 137.0, 128.3 (2), 128.1, 125.3 (2), 122.1, 99.1, 69.0, 61.5 (2), 51.0, 38.8, 37.1, 14.1 (2); HRMS *m/z* 344.1617 (calcd for $C_{20}H_{24}O_5$ 344.1624).

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$BF_3{\cdot}OEt_2$ Catalyzed Reaction of Donor-Acceptor Cyclobutanes with Terminal Alkynes: One Step Access to 2,3-Dihydrooxepines