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# DABCO-Catalyzed 1,4-Bromolactonization of Conjugated Enynes: Highly Stereoselective Formation of a Stereogenic Center and an Axially Chiral Allene

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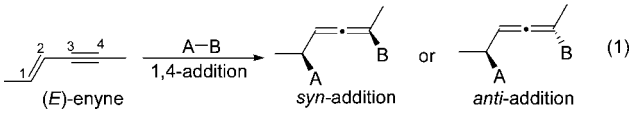
Stereoselective functionalization of alkenes and alkynes is one of the most influential fields in organic chemistry. While the regio- and stereoselectivity of the addition to alkenes or alkynes have been studied extensively for the formation of adjacent stereogenic centers or geometrically defined alkenes, little is known about the 1,4-addition across conjugated enynes, in which a chiral allene can be cointroduced with a stereogenic center (eq 1):[1] We herein report our recent discovery

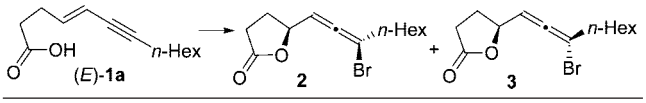



(1)

of a DABCO-catalyzed, highly regio- and diastereoselective 1,4-bromolactonization of conjugated enynes. Thus, synthetically valuable bromoallenes[2] and lactones can be prepared efficiently and selectively.[3]

Halogen-promoted addition of nucleophiles to alkenes is one of the most fundamental reactions in chemistry and is widely used in organic synthesis.[4] Among all halocyclizations, halolactonization is arguably the most versatile since the resulting lactone can easily be elaborated.[5] Although several 1,4-bromoetherifications of conjugated enynes have been reported in natural product synthesis,[6] low diastereomeric ratios were generally observed for the newly generated stereogenic center and axially chiral allene. To the best our knowledge, the 1,4-bromolactonization of conjugated enynes is hitherto unknown, even in the nonstereoselective format.

***Table 1.*** Screening of Catalysts for Enyne Bromolactonization[a]

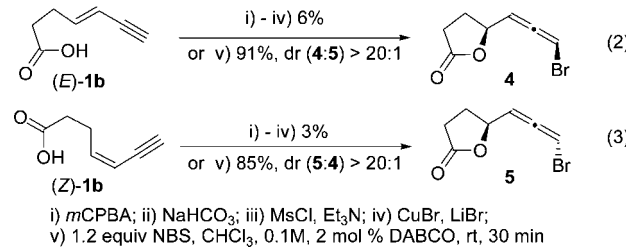



| entry | catalyst | conversion (%)[b] | dr[b] |
|---|---|---|---|
| 1 | none | ~0 | — |
| 2 | $Ph_3P$ | 69 | 2:1 |
| 3 | DMF | 94 | 3:1 |
| 4 | HMPA | 88 | 1:1 |
| 5 | HMPT | 100 | 3:1 |
| 6 | pyridine | 100 | 5:1 |
| 7 | DMAP | 100 | 13:1 |
| 8 | 2,6-lutidine | 100 | 3:1 |
| 9 | $Et_3N$ | 32 | 10:1 |
| 10 | DBU | 92 | 10:1 |
| **11** | **DABCO** | **93** | **>20:1** |

[a] Conditions: 1.2 equiv of NBS, $CDCl_3$, 0.02 M, 10 mol % catalyst, rt, 30 min. [b] Estimated by $^1H$ NMR.

When enynic acid (*E*)-**1a** was treated with 1.2 equiv of NBS, no reaction occurred (Table 1, entry 1). Nucleophilic catalysts have been used to facilitate the addition of halogens and nucleophiles to olefins through the formation of more reactive halogen electrophiles.[7] A highly enantioselective halocyclization of alkenes mediated by stoichiometric amounts of chiral nucleophilic reagents has also been reported.[7d] In the present case, good conversions were observed after the addition of 10 mol % phosphine, amide, or amine catalyst (entries 2−11). Interestingly, although a broad range of diastereomeric ratios was observed, all of the catalysts except HMPA (entry 6) favored the same isomer. Amine catalysts were more selective than others. DABCO (entry 11) afforded essentially one diastereomer (dr > 20:1 based on NMR analysis of the crude mixture). We did not observe any 5-exo or 6-endo cyclization products resulting from 1,2-addition to enyne (*E*)-**1a**, indicating excellent regioselectivity.

To assign the relative stereochemistry of the enyne bromolactonization products and hence the mode of 1,4-addition (i.e., syn versus anti), we prepared bromoallenyl lactones **4** and **5** from the corresponding enynic acids (*E*)-**1b** and (*Z*)-**1b** via a four-step sequence: epoxidation, lactonization, mesylation, and copper-mediated anti-$S_N2'$ substitution (eqs 2 and 3).[8] By comparing the results from the four-




(2)

(3)

i) *m*CPBA; ii) $NaHCO_3$; iii) MsCl, $Et_3N$; iv) CuBr, LiBr;
v) 1.2 equiv NBS, $CHCl_3$, 0.1M, 2 mol % DABCO, rt, 30 min

step protocol and the DABCO-catalyzed cyclizations, we concluded that in the presence of 2 mol % DABCO, both enynes (*E*)-**1b** and (*Z*)-**1b** underwent highly selective *syn*-1,4-bromolactonization to give products with complementary stereochemistries.[9]

We then explored the scope of the DABCO-catalyzed enyne bromolactonization. Enynic acids **1** (Table 2, entries 1−16) were prepared in one to five steps[9] from commercially available conjugated enynes, Sonogashira cross-coupling,[10] or the addition of terminal alkynes to ynoates developed by Trost.[11] Five-membered bromoallenyl-substituted lactones were obtained with high stereoselectivity from (*E*)-enynes with various terminal substituents (entries 1−4). The sterically demanding *tert*-butyl group decreased the dr to ~10:1 (entry 3). Substrate (*E*)-**1e** with a sterically bulky trimethylsilyl group, however, afforded allene **8** with >20:1 dr (entry 4). Six-membered lactones could also be prepared stereoselectively from (*E*)-enynes (entries 5 and 6). Heteroatom linkers such as oxygen or tosylamide could be tolerated (entries 7−9). Cyclization products with complementary stereochemistry were stereoselectively obtained from substituted (*Z*)- and (*E*)-enynic acids (entries 10−12 vs 1, 2, and 8).

After successful preparation of di- and trisubstituted allenes, we then examined the formation of tetrasubstituted allenes (entries 13−16). Both allenes **16** and **18** were obtained with high stereoselectivity but in low yields. In each case, we observed a significant amount of lactone derived from 1,2-addition to the alkene. We reasoned that the methyl substituent increased the electron density of the alkene, causing the electrophilic bromine to react with the alkene preferentially. We



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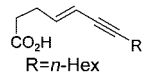
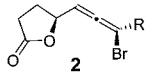
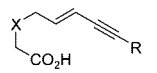
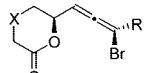
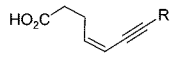
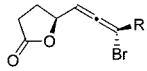
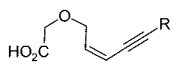
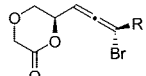
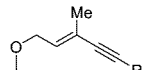
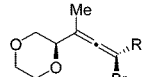
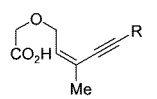
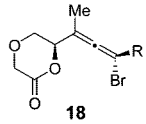
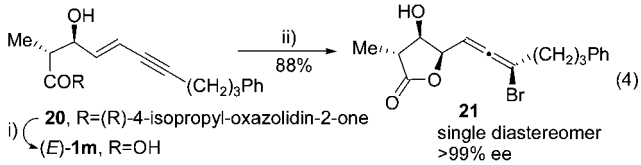
hypothesized that an electron-donating substituent on the alkyne could switch the regioselectivity back to 1,4-addition. Indeed, enynic acids (*E*)-**1l** and (*Z*)-**1l** with a triethylsilyl substituent underwent 1,4-addition selectively despite the steric bulk of the silyl group, yielding the corresponding tetrasubstituted allenes **17** and **19** with complementary stereochemistry (entries 14 and 16). Substituted 1-bromo-1-silylallenes **8**, **10**, **17**, and **19** were then prepared efficiently.[3]

***Table 2.*** Scope of the Stereoselective Enyne Bromolactonization[a]

| entry | | enyne substrate | allene product | yield | dr[b] |
|---|---|---|---|---|---|
| | |  |  | | |
| 1 | (*E*)-**1a** | R=*n*-Hex | **2** | 90% | >20:1 |
| 2 | (*E*)-**1c** | R=Ph(CH$_2$)$_2$ | **6** | 80% | >20:1 |
| 3 | (*E*)-**1d** | R=*t*-Bu | **7** | 83% | 10:1 |
| 4 | (*E*)-**1e** | R=TMS | **8** | 74% | >20:1 |
| | |  |  | | |
| 5 | (*E*)-**1f** | X=CH$_2$,R=Ph(CH$_2$)$_3$ | **9** | 86% | >20:1 |
| 6 | (*E*)-**1g** | X=CH$_2$, R=TMS | **10** | 67% | >20:1 |
| 7 | (*E*)-**1h** | X=O, R=H | **11** | 86% | >20:1 |
| 8 | (*E*)-**1i** | X=O, R= Ph(CH$_2$)$_3$ | **12** | 76% | >20:1 |
| 9[c] | (*E*)-**1j** | X=NTs, R=H | **13** | 97% | >20:1 |
| | |  |  | | |
| 10 | (*Z*)-**1a** | R=*n*-Hex | **3** | 87% | >20:1 |
| 11[c] | (*Z*)-**1c** | R=Ph(CH$_2$)$_2$ | **14** | 80% | >20:1 |
| | |  |  | | |
| 12 | (*Z*)-**1i** | R=Ph(CH$_2$)$_3$ | **15** | 74% | >20:1 |
| | |  |  | | |
| 13 | (*E*)-**1k** | R=Ph(CH$_2$)$_3$ | **16** | 21%[d] | >20:1 |
| 14 | (*E*)-**1l** | R=TES | **17** | 74% | >20:1 |
| | |  |  | | |
| 15 | (*Z*)-**1k** | R=Ph(CH$_2$)$_3$ | **18** | 17%[d] | >20:1 |
| 16 | (*Z*)-**1l** | R=TES | **19** | 72% | >20:1 |

[a] Conditions: 1.2 equiv of NBS, $CHCl_3$, 0.1 M, 2 mol % DABCO, rt unless noted otherwise. [b] Estimated by $^1$H NMR. [c] Using 10 mol % DABCO, 0.02 M. [d] See the text for details.

Cyclization of substrate (*E*)-**1m** derived from a single isomeric aldol product **20**[9,12] led to allene **21** as a single diastereomer with over 99% ee (eq 4), suggesting nearly perfect diastereoselectivity for the newly generated stereogenic center with respect to both pre-existing stereogenic centers[13] and the axially chiral allene.




(4)

i) LiOH, $H_2O_2$, 74%; ii) 1.2 equiv NBS, $CHCl_3$, 2 mol % DABCO, rt.

In summary, we have discovered a novel DABCO-catalyzed, highly regio- and diastereoselective 1,4-bromolactonization of conjugated enynes to generate lactones together with di-, tri-, or even tetrasubstituted allenes under mild conditions. Further investigations into the origin of the catalyst-controlled syn selectivity for 1,4-addition to conjugated enynes, synthetic applications of bromoallenyl lactones in the synthesis of natural products, and catalytic diastereo- and enantioselective[14] 1,4-bromolactonization of conjugated enynes are underway.

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**Supporting Information Available:** Experimental procedures and characterization data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Our preliminary study has demonstrated that 20 mol % cinchonidine catalyst can induce 58% ee and still retain high diastereoselectivity (dr > 20:1) in the formation of compound **15**.

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