Communication

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Enantioselective, Desymmetrizing Bromolactonization of Alkynes

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Supporting Information Placeholder

ABSTRACT: Asymmetric Bromolactonizations of alkynes are possible using a desymmetrization approach. The commercially available catalyst $(DHQD)_2PHAL$ promotes these cyclizations in combination with cheap NBS as bromine source to give bromoenol lactones in high yield and with high enantioselectivity. The bromoenol lactone products, containing a tetra-substituted alkene and a quaternary stereocenter, are valuable building blocks for synthetic chemistry.

The first halolactonization reactions of alkenoic acids have been discovered more than a century ago.[1] Since then halolactonizations and related halocyclizations have been widely used in organic synthesis due to the mild reaction conditions, high chemo- and regioselectivity and functional group tolerance.[2] In many cases, halolactonizations proceed with high diastereoselectivities if the starting material already contains a stereogenic element (substrate control).[3] However, reagent-controlled stereoselective variants have been missing and only recently such methods have been developed.[3,4] Early stoichiometric attempts led only to moderate enantioselectivities or showed a limited substrate scope.[5] Catalytic, enantioselective iodoetherifications were described by Kang using transition metal salen complexes as catalyst, but the application of this method to iodolactonizations requires large amounts of catalysts.[6] An asymmetric, organocatalytic method was developed by the Borhan group in 2010 showing that dimeric chinchona alkaloid derivatives such as $(DHQD)_2PHAL$ **1a** (Figure 1) are efficient organocatalysts for highly enantioselective chlorolactonizations of alkenoic acids.[7] At about the same time organocatalysts for highly enantioselective bromo- and iodolactonizations were reported by several other groups including thiocarbamates (Yeung)[8], trisimidazolines (Fujioka)[9] and ureas (Jacobsen)[10]. This rapid development has continued and several more structurally different organocatalysts for enantioselective halolactonizations have been reported since then.[11] Some of these catalysts are also applicable to related asymmetric halocyclization reactions of amides.[12] Similarly, new catalysts have been described for other asymmetric alkene halogenations such as haloetherifications, halogen-induced semipinacol rearrangements and alkene dihalogenations.[13] Asymmetric halolactonizations have not only been described for alkenes, but also for conjugated (*Z*)-enynes.[14] Tang et al. demonstrated that the halogenation in this case takes place at the C-C-triple bond followed by vinylogous addition of the nucleophile to give chiral, brominated allenes. However, enantioselective halocyclizations of simple, non-conjugated alkynes have not been reported. Herein, we disclose our findings on organocatalytic halocyclizations of diynoic acids which have led to the development of highly enantioselective, desymmetrizing halolactonizations of non-conjugated alkynes.

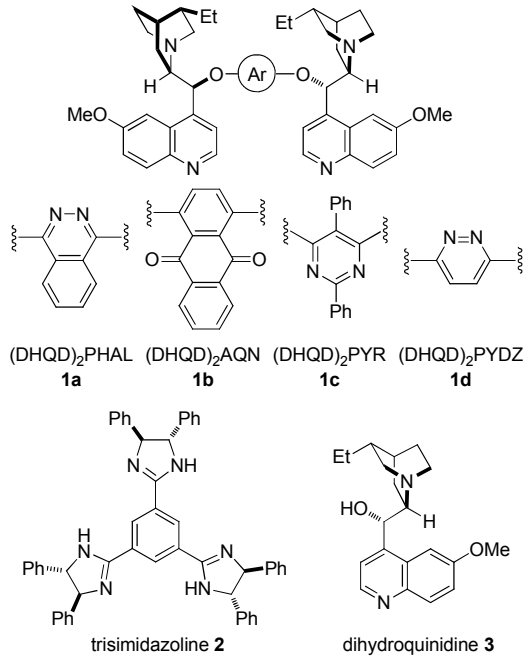
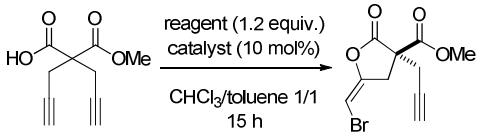


Figure 1. Organocatalysts used in enantioselective halogenations.

Bromination of a simple alkynoic acid using NBS leads most likely to the formation of a bromirenium ion (the analog of the bromonium ion) followed by a lactonization to give exclusively the (*E*)-alkene.[15] As the bromirenium ion and the resulting alkene are non-stereogenic, the resulting 2-bromoenol lactone is formed without a new stereocenter. To make an asymmetric cyclization possible we chose a desymmetrization approach[16] on diynoic acids using model substrate **4a**, easily available by dipropargylation/monohydrolysis of dimethyl malonate. Upon treatment with 1.2 equivalents NBS diynoic acid **4a** undergoes a 5-*exo* bromolactonization to give chiral bromoenol lactone **5a** containing a quaternary stereocenter in the backbone (Table 1). Without a catalyst this reaction is rather slow at low temperature. Upon addition of trisimidazoline catalyst **2** complete and selective conversion to

(*E*)-bromoenol lactone **5a** was observed in less than 15 h. The product was formed with a small, but significant enantiomeric excess (58:42 er, table 1, entry 1), showing that enantioselective halolactonizations of alkynes are possible. Significantly improved enantiomeric ratios were obtained using $(DHQD)_2PHAL$ **1a** as catalyst (83:17 er, entry 2). Other dimeric chinchona alkaloid-derived catalysts or simple monomeric dihydroquinidine **3** led to mixed results. The pyridazine-bridged dihydroquinidine dimer $(DHQD)_2PYDZ$ **1d** catalyzed the formation of product **5a** with good yield and a moderate er (74:26, entry 5). Monomeric dihydroquinidine **3** or dimeric derivatives containing non-pyridazine bridges were ineffective and gave only low yields and selectivities (entries 3, 4, 7). This points to the importance of the pyridazine unit to achieve high enantioselectivities. The pseudoenantiomeric catalyst $(DHQ)_2PHAL$ **1e** performed similar to **1a** providing the product with slightly lower enantioselectivity (25:75 er, entry 6). The use of alternative halogen sources did not give improved results. The chlorinating agent NCS did not induce a cyclization (entry 8). NIS on the other hand initiated iodolactonization to give the iodoenol lactone **I-5a** with an enantioselectivity lower than in the corresponding bromolactonization (74:26 er, entry 9). Substituting NBS for other brominating agents such as DBDMH had only minor effects on the yield and enantioselectivity (entry 10, see also SI). A further improvement in enantioselectivity could be achieved by carefully controlling the reaction conditions including solvent and temperature (entries 11-14). A reaction temperature of -30°C proved to be optimal while the reaction was best conducted in a mixture of a chlorinated solvent ($CHCl_3$) and a hydrocarbon (toluene or *n*-hexane, see also SI). The product **5a** was rather labile towards hydrolysis and could be isolated in pure form only, when a very short silica column was used for chromatography. Nevertheless, under the optimized reaction conditions (1.2 equiv. NBS, 10 mol% $(DHQD)_2PHAL$, -30 °C, $CHCl_3$/*n*-hexane 1/1) the product **5a** was obtained in 81% yield and with an enantioselectivity of 86:14 er. The absolute configuration of **5a** was assigned to be 3*R* based on its crystal structure.[17]

Table 1. Halolactonization of dialkynoic acid 4a



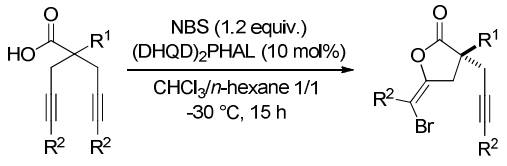
4a **5a**

Entry	Reagent	Catalyst	T (°C)	Yield (%)[a]	er
1	NBS	**2**	-78 - rt	86	58:42
2	NBS	**1a**	-78 - rt	77	83:17
3	NBS	**1b**	-78 - rt	15	48:52
4	NBS	**1c**	-78 - rt	17	53:47
5	NBS	**1d**	-78 - rt	64	74:26
6	NBS	**1e**	-78 - rt	56	25:75
7	NBS	**3**	-78 - rt	30	52:48
8	NCS	**1a**	-78 - rt	-[b]	-
9	NIS	**1a**	-78 - rt	99 (**I-5a**)	74:26
10	DBDMH	**1a**	-78 - rt	70	83:17
11	NBS	**1a**	0	88	80:20
12	NBS	**1a**	-30	79	86:14
13	NBS	**1a**	-50	45	76:24
14[c]	NBS	**1a**	-30	81	86:14

[a]Reactions were conducted on a 0.1 mmol scale; isolated yield. [b]less than 5% conversion. [c]Reaction conducted in $CHCl_3$/*n*-hexane 1/1.

Under the optimized conditions the scope of the reaction was investigated (Table 2). Dialkynoic acids with terminal alkynes such as **4a** or **4f** gave the products **5a** and **5f**, respectively, with good yields and in good enantioselectivity (entries 1, 6). However, if the alkynes were internal alkynes carrying an alkyl or aryl substituent, the products were formed with significantly higher enantiomeric ratios. Methyl substituted alkynes led to the formation of the products with generally very good yields (above 90%) and excellent enantioselectivity above 95:5 er (entries 2, 7, 10, 11). Malonate **4c** with an ethyl-substituted triple bond yielded the product **5c** again with very good yield and good enantioselectivity (88:12 er, entry 3). Alkynoic acids with electron neutral or electron deficient aromatic substituents on the alkynes cyclized with good yields and high enantioselectivity as well (entries 4, 5, 8, 9). Interestingly, in these cases the catalyst did not only influence the stereoselectivity of the reaction, but also the regioselectivity. If, for example, substrate **4h** was reacted with NBS without any catalyst, a sluggish cyclization occurred leading to a mixture of regioisomeric products resulting from 5-*exo* or the 6-*endo* cyclization. Upon addition of the $(DHQD)_2PHAL$ **1a** catalyst, exclusively 5-*exo* cyclization to the product **5h** was observed again. The fourth substituent at the quarternary carbon atom (R^1) had a smaller influence on the reaction and a range of different groups were well tolerated. The enantioselectivities observed with starting materials derived from malonic acid ($R^1 = CO_2Me$, entries 1-5), phenyl acetic acids (R^1 = Ph, C_6H_4R, entries 6-11) or even acetic acid (R^1 = H, entry 12) were similar and clearly more depended on the alkyne substituent. However, when substituent R^1 was a CH_2OH group carrying a 4-bromobenzoyl protecting group, even a terminal alkyne reacted to the product **5m** with very high enantioselectivity (er 97:3, entry 13). As mentioned earlier, only a pseudoenantiomer of **1a**, $(DHQ)_2PHAL$ **1e**, is commercially available. To investigate, if the pseudoenantioneric catalyst **1e** is equally efficient as **1a**, we cyclized starting materials **5b** and **5i** using this catalyst. The enantiomeric products ***ent*-5** were obtained with slighty lower, but still very good yields and in almost equally high enantioselectivities when compared to the standard conditions.

Table 2. Reaction scope



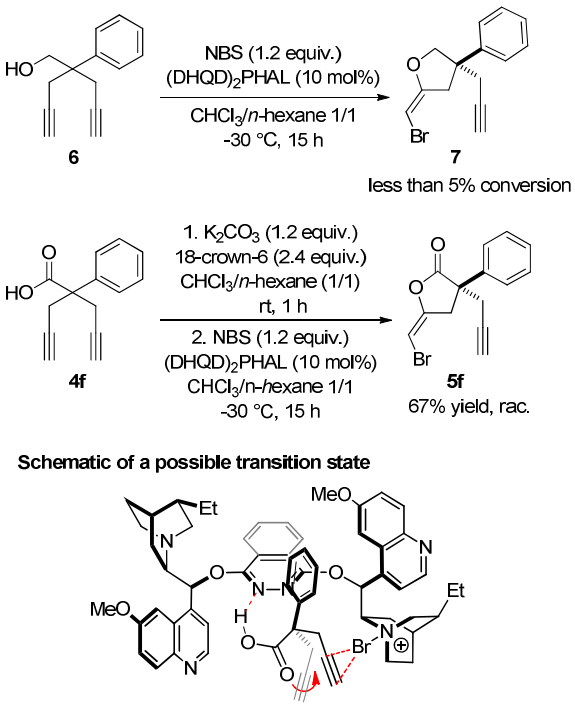
4 **5**

Entry	Acid	R^1	R^2	Yield (%)[a]	er
1	**4a**	CO_2Me	H	**5a**, 79	86:14
2	**4b**	CO_2Me	Me	**5b**, 91	95:5
3	**4c**	CO_2Me	Et	**5c**, 90	88:12
4	**4d**	CO_2Me	Ph	**5d**, 83	98:2
5	**4e**	CO_2Me	4-ClC_6H_4	**5e**, 92	98:2
6	**4f**	Ph	H	**5f**, 90	85:15
7	**4g**	Ph	Me	**5g**, 98	96:4
8	**4h**	Ph	Ph	**5h**, 94	92:8
9	**4i**	Ph	4-ClC_6H_4	**5i**, 92	96:4

10	**4j**	4-FC_6H_4	Me	**5j**, 98	96:4
11	**4k**	3-ClC_6H_4	Me	**5k**, 90	95:5
12	**4l**	H	Me	**5l**, 95	93:7
13[b]	**4m**	CH_2OR^3	H	**5m**, 82	97:3
14[c]	**4b**	CO_2Me	Me	***ent*-5b**, 86	5:95
15[c]	**4i**	Ph	4-ClC_6H_4	***ent*-5i**, 76	6:94

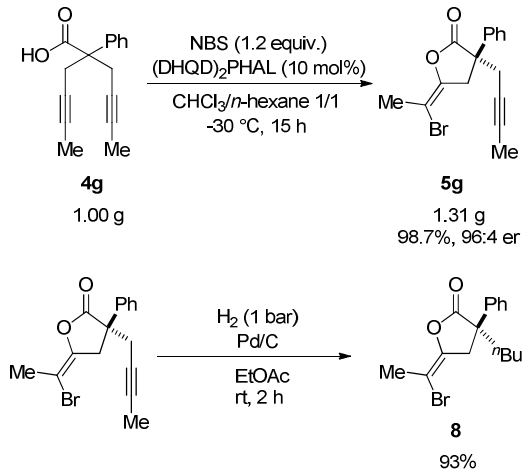
[a]Reactions were conducted on a 0.3 mmol scale; isolated yield. [b]R^3 = 4-BrBz. [c]$(DHQ)_2PHAL$ **1e** was used instead of $(DHQD)_2PHAL$ **1a**.

Scheme 1. Halocyclizations of diynol 6 and the potassium salt of 4f. Schematic of a possible transition state.



From a mechanistic point of view, enantioselective halolactonizations of alkynes are highly interesting. The halogenation of an alkene leads to the formation of a halonium ion, which is in most cases already chiral. However, the corresponding halirenium ions formed by the halogenation of an alkyne are planar and therefore achiral. This leads to two possible mechanistic scenarios for our desymmetrizing alkyne halolactonizations: the catalyst could direct an initial irreversible halogenation to only one of the two alkynes, creating a stereocenter remote from the side of halogenation, followed by a subsequent cyclization. In the case of such an irreversible, catalyst-mediated enantioselective halogenation, only rarely precedented in the literature[16], the subsequent reaction should not be of high importance. Alternatively, the formation of the halirenium ion might be reversible and the catalyst is activating the carboxylic acid group for a cyclization onto only one of the two possible, enantiomeric halirenium ions formed in equilibrium. To better understand the function of the catalyst we conducted several experiments. When diynol **6** was treated with NBS, no reaction was observed with or without catalyst **1a** (Scheme 1, top). This confirms that the activation of the carboxylic acid nucleophile plays a significant part in this reaction. If we assume that catalyst's **1a** most important function is to bind and activate the carboxylic acid group of the starting material via a hydrogen bond or deprotonation, than the prior deprotonation of the carboxylic acid group should abolish catalyst activity. To test this hypothesis we treated diynoic acid **4f** with two equivalents of potassium carbonate and 18-crown-6 to prepare a soluble potassium salt in situ and cyclized this salt under standard reaction conditions. The product **5f** was obtained in good yield (67 %), but as a racemate (Scheme 1, middle). The interaction of the catalyst with the carboxylic acid group was further substantiated by NMR experiments. Upon mixing one equivalent of catalyst **1a** with one equivalent of diynoic acid **4a** the alkynyl and propargyl protons of **4a** split into two sets of signals indicating that these groups have become diastereotopic upon binding of diynoic acid **4a** to the catalyst **1a**. (see SI for details). Our experiments show that the interaction of the catalyst **1a** with the carboxylic acid group is very important supporting the second mechanistic scenario.[18] This interaction might take place at the pyridazine nitrogen, as only pyridazine-bridged catalysts (**1a**, **1d**, **1e**) led to good enantioselectivities. However, that does not mean that the activation of the carboxylic acid is the only function of catalyst **1a** and it is possible that it is a bifunctional catalyst activating the brominating agent NBS as well as demonstrated by Borhan for chlorinating agents.[7,19] A schematic drawing of a possible transition state, in line with Borhan's[7] and Nicolaou's[13g] proposals, indicates the activation of the carboxylic acid by the pyridazine unit (Scheme 1, bottom).

Scheme 2. Gram scale synthesis of 5g and subsequent selective hydrogenation.



To demonstrate the practicality of our protocol we conducted a gram scale cyclization experiment. Diynoic acid **4g** (1.00 g, 4.16 mmol) was cyclized under standard conditions to give 1.31 grams (4.10 mmol) of bromoenol lactone **5g** (Scheme 2, top). Yield and enantioselectivity remain as high as in small scale experiments. Bromoenol lactone **5g** is a valuable building block for further modification. For example, the C-C-triple bond can be selectively hydrogenated to give butyl-substituted bromenol lactone **8** in excellent yield (93%) while leaving the sensitive bromoenol moity intact (Scheme 2, bottom).

In conclusion, we present herein the first highly enantioselective halolactonization of simple, non-conjugated alkynoic acids. The reaction allows the rapid and stereoselective synthesis of bromoenol lactones containing a tetra-substituted alkene and an all-carbon quaternary stereocenter. These molecules are not only of interest as valuable building blocks for synthetic chemistry, but also in medicinal chemistry. 2-Haloenol lactones are covalent inhibitors of serine proteases such as chymotrypsin functioning

through a unique mechanism-based pathway.[15,20] Our method allows the rapid, stereoselective synthesis of these compounds.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all compounds. Details on the X-ray structure determination, CD spectra and DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(16) For desymmetrizing halolactonizations of alkenes, see: Kitagawa, O.; Taguchi, T. *Synlett* **1999**, 1191.

(17) See Supporting Information for details. All other compounds were assigned accordingly. This assignment is supported by the CD spectrum compound **5i** which was calculated using DFT methods (see Supporting Information for details).

(18) Note that also Fujioka's trisimidazoline catalyst **2** is able to induce a small, but significant enantioselectivity in our alkyne cyclizations (table 1, entry 1). This catalyst does not promote an enantioselective halogenation, but a selective activation of the carboxylic acid group for cyclization in alkene bromolactonizations.[9]

(19) For an NMR spectrum of a 1:1 mixture of catalyst **1a** and NBS showing moderate shifts of some signals see SI.

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