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Enantioselective Bromolactonization of Conjugated (*Z*)-Enynes

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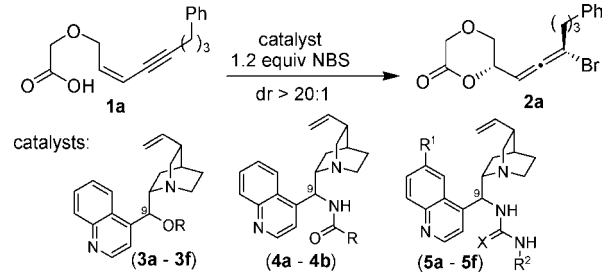
Halogen promoted addition of nucleophiles to alkenes represents one of the most fundamental reactions in chemistry and is widely used in organic synthesis for the stereoselective introduction of functional groups.[1] However, the catalytic enantioselective addition of halogen and nucleophile to unactivated alkenes remains elusive despite recent impressive progress in asymmetric catalysis. A few highly enantioselective reactions were developed for the halocyclization of alkenes promoted by chiral electrophiles comprising halonium cations.[2−4] Up to 93% ee was obtained for iodocyclization of γ-hydroxy-*cis*-alkenes using Salen-Co or Salen-Cr catalysts.[2,3] Iodocyclization of polyprenoids with up to 99% ee was achieved with a stoichiometric amount of chiral phosphoramidites.[4] Among all halocyclizations, halolactonization is arguably the most versatile since the resulting lactone can be easily elaborated.[5] Although there have been several examples of enantioselective halolactonization, low enantioselectivity was generally observed prior to our study.[6]

We recently discovered a DABCO-catalyzed highly diastereoselective enyne bromolactonization reaction.[7] Unlike the well-known *anti*-1,2-bromolactonization of alkenes, *syn*-1,4-bromolactonization of enynes occurred in the presence of DABCO catalyst. Herein, we report a bifunctional catalyst promoted highly enantioselective bromolactonization of conjugated (*Z*)-enynes for the preparation of versatile bromoallenes[8] and lactone heterocycles with high optical purity.

Our initial studies revealed that 20 mol % of cinchonidine **3a**,[9] which has a bridgehead nitrogen similar to DABCO, could induce moderate ee for product **2a** from *cis*-enyne **1a** and still retain high diastereoselectivity (dr > 20:1) (entry 1, Table 1).[10] The ee's dropped significantly with 9-alkoxy, 9-siloxy, and 9-epimeric cinchonidines (entries 2−6), suggesting that the 9-hydroxyl group of **3a** plays an important role for the induction of enantioselectivity and is likely served as a hydrogen bond donor rather than an acceptor.

We then converted the 9-hydroxyl group to amide, urea, and thiourea, which are strong hydrogen bond donors (entries 7−16).[11] Amides **4a** and **4b** provided low enantioselectivity (entries 7 and 8). Catalysts with a urea group improved the enantioselectivity significantly (entries 9, 10, and 12).[12] Notably, ureas **5b** and **5d**, which are first reported here, performed better than known catalyst **5a**.[12] It is also interesting to note that urea **5b** with a 9*S* configuration performed much better than its 9-epimer **5c**. This is opposite to the trend observed for catalyst **3**, where the 9*R* configuration performed better than 9*S* (**3a** versus **3f**). Surprisingly, thiourea catalyst **5e** with the 9*S* configuration was not able to catalyze the reaction (entry 13). Full conversions and comparable rates were observed for most catalysts in Table 1 except **5e**. Urea catalyst **5d** was then chosen for further optimization in different solvents. Of the solvents surveyed, including chloroform, methylene chloride, 1,2-dichloroethane, toluene, ethyl acetate, and acetonitrile, 1,2-dichloroethane gave the highest isolated yield and ee (entry 17).[10] When the catalyst loading was decreased to 10 mol %, the ee dropped from 89% to 80% (entry 18).

Table 1. Screening of Catalysts and Conditions[a]



entry	catalyst	*ee* %[b]
1	**3a**, (9*R*), R = H	−58
2	**3b**, (9*R*), R = Me	0
3	**3c**, (9*R*), R = triphenylsilyl	5
4	**3d**, (9*R*), R = Bn	21
5	**3e**, (9*R*), R = 1-naphthyl	24
6	**3f**, (9*S*), R = H	−6
7	**4a**, (9*S*), R = Ph	30
8	**4b**, (9*R*), R = Ph	0
9	**5a**, (9*S*), R_1 = H, X = O, R_2 = 3,5-$(CF_3)_2C_6H_3$	70
10	**5b**, (9*S*), R_1 = H, X = O, R_2 = Ts	75
11	**5c**, (9*R*), R_1 = H, X = O, R_2 = Ts	10
12	**5d**, (9*S*), R_1 = OMe, X = O, R_2 = Ts	80
13	**5e**, (9*S*), R_1 = H, X = S, R_2 = 3,5-$(CF_3)_2C_6H_3$	NR
14	**5f**, (9*R*), R_1= H, X = S, R_2 = 3,5-$(CF_3)_2C_6H_3$	−13
15	**5g**, (9*S*), R_1 = H, X = O, R_2 = Ph	10
16	**5h**, (9*S*), R_1 = H, X = O, R_2 = *t*-Bu	19
17[c,d]	**5d**	**89**
18[c]	**5d** (10 mol %)	80

[a] Conditions: To a solution of enyne **1** and catalyst (20 mol %) in $CHCl_3$ was added NBS, and the solution was stirred at rt unless noted otherwise. [b] Products with negative enantiomeric excess (ee) have *ent*-**2a** as the major isomer. [c] Solvent is $ClCH_2CH_2Cl$. [d] 72% isolated yield.

It has been proposed that halogenation reagents could be activated by chiral nucleophilic promoters[4] or Lewis acids.[13] In the case of catalyst **5d**, either the quinuclidine nitrogen or urea group may activate NBS via formation of a new electrophilic brominating species or hydrogen bonding respectively. When we premixed NBS (1.2 equiv) and **5d** (20 mol %) in $ClCH_2CH_2Cl$ and stirred for 20 min before the addition of acid **1a**, the ee of product **2a** dropped from 89% to 54% without significant change of the yield. A longer premixing time (4 h) further deteriorated the ee to 26%. The reaction between NBS and catalyst **5d** appeared to be an undesired pathway. Although other mechanisms cannot be ruled out at present, activation of NBS by hydrogen bonding with urea and/or protonated amine is more consistent with the above results and data in Table 1.

We then explored the scope of the catalytic enantioselective enyne bromolactonization (Table 2). High enantioselectivity was generally observed for *cis*-enynes with various terminal substituents

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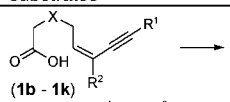
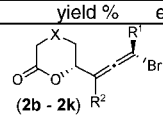
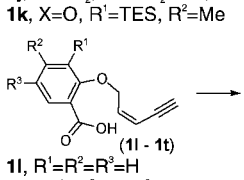
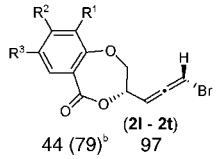
Table 2. Scope of the Enantioselective Enyne Bromolactonization[a]

entry	substrates	yield %	ee %
	 (**1b - 1k**)  (**2b - 2k**)		
1	**1b**, X=O, R^1=H, R^2=H	71	90
2	**1c**, X=O, R^1=*n*-Pr, R^2=H	77	90
3	**1d**, X=O, R^1=*i*-Pr, R^2=H	72	90
4	**1e**, X=O, R^1=*t*-Bu, R^2=H	76	90
5	**1f**, X=O, R^1=TES, R^2=H	87	88
6	**1g**, X=O, R^1=CH_2OPh, R^2=H	70	90
7	**1h**, X=O, R^1=CH_2OPMB, R^2=H	70	92
8	**1i**, X=NTs, R^1=H, R^2=H	62	93
9	**1j**, X=CH_2, R^1=CH_2OPh, R^2=H	82	80
10	**1k**, X=O, R^1=TES, R^2=Me	86	81
	 (**1l - 1t**)  (**2l - 2t**)		
11	**1l**, R^1=R^2=R^3=H	44 (79)[b]	97
12	**1m**, R^1=R^3=H, R^2=OMe	see text	
13	**1n**, R^1=R^3=H, R^2=Cl	72	98
14	**1o**, R^1=R^3=H, R^2=CF_3	74	99
15	**1p**, R^1=R^2=H, R^3=$CH_3C(O)$	68	97
16	**1q**, R^1=R^3=Br, R^2=H	85	94
17	**1r**, R^1=R^2=H, R^3=NO_2	80	97
18	**1s**, R^2=R^3=H, R^1=NO_2	88	95
19	**1t**, R^1=R^3=H, R^2=NO_2	76	98

[a] Conditions: To a solution of **1** and **5d** (20 mol %) in $ClCH_2CH_2Cl$ was added NBS (1.2 equiv), and the solution was stirred at rt for 0.5−10 h. [b] The yield of 79% is based on recovered starting material.

(entries 1−7, Table 2). The observed dr's were >20:1 for almost all substrates except **1e** with a dr ≈ 10:1.[7] Nitrogen and carbon linkers could also be tolerated (entries 8 and 9). The reaction time became longer for substrates with electron-withdrawing groups on the terminal position (entries 6, 7, and 9). Trisubstituted olefin (*Z*)-**1k** yielded tetrasubstituted allene **2k** in 81% ee (entry 10), while the corresponding (*E*)-**1k** yielded racemic products.

Cyclization of substrate **1l** under optimized conditions provided lactone **2l** in high enantioselectivity albeit in lower conversion (entry 11). Surprisingly, mainly 1,2-addition products were observed for methoxy substituted substrate **1m**. On the other hand, various electron-withdrawing groups improved the conversion and still retained the high enantioselectivity, with ee's ranging from 94% to 99% (entries 13−19).

In some previous cases (e.g., entries 6, 7, and 9), the reaction required a much longer time for completion using DABCO compared to urea **5d** as the catalyst. However, no reaction occurred for substrate **1n** using 20 mol % of either DABCO or simple urea BnNHC(O)NHTs alone. Addition of both DABCO (20 mol %) and urea BnNHC(O)NHTs (20 mol %) provided 12% of lactone (±)-**2n**, and 82% of acid **1n** were recovered after 12 h. Other substrates also gave the corresponding racemic products in similar yields under the above conditions (e.g., 12% of (±)-**2o**, 20% of (±)-**2r**, and 9% of (±)-**2t**). These results suggest that both quinuclidine and urea groups of catalyst **5d** are critical for activity in these cases. Although the detailed mechanism has not been clarified, we propose that catalyst **5d** may serve as a bifunctional catalyst[12] to activate the system via deprotonation of the carboxylic acid and formation of hydrogen bonds with NBS.

The relative stereochemistry of the products and the absolute stereochemistry of the bromoallenes were assigned based on our previous study[7] and Lowe's rule for allenes respectively.[14] The X-ray structure of lactone **2n** further confirmed our assignment.[15]

In summary, we have developed a bifunctional catalyst promoted highly enantioselective bromolactonization of *(Z)*-enynes.[16] We anticipate that further investigation of this class of bifunctional catalysts would lead to novel entries for other halogen promoted enantioselective reactions.

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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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(15) See Supporting Information for details.
(16) Bromolactonization of simple olefins catalyzed by **5d** yielded nearly racemic products in a preliminary study described in the Supporting Information.

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