Stereoselective Halocyclization of Alkenes With *N*-Acyl Hemiaminal Nucleophiles

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ABSTRACT Halocyclization of alkenes was realized using *N*-acylhemiaminal nucleophiles. High diastereoselectivity could be achieved for the formation of three stereogenic centers in this halogen-mediated cyclization reaction. We also demonstrated that enantioselective bromocyclization of alkenes using *N*-acylhemiaminal nucleophiles was possible. *Chirality 25:805–809, 2013.* © 2013 Wiley Periodicals, Inc.

KEY WORDS: halocyclization; hemiaminal; stereoselective; alkene

INTRODUCTION

The development of chemo-, regio-, and stereoselective addition reactions to alkenes is of fundamental importance in organic chemistry. Halogen-promoted addition of nucleophiles to unsaturated C-C bonds represents one of the most powerful methods in organic synthesis and is widely used for the introduction of diverse functionalities to organic compounds.[1–4] The resulting carbon-halogen bonds are not only present in numerous halogen-containing natural products[5–9] but also serve as useful handles for the introduction of other functional groups. In addition to carbon-halogen bonds, the halogen-promoted addition reactions may also provide various other bond types (e.g., C-O, C-N, and C-C) depending on the choice of nucleophiles. We herein introduce hemiaminals as a new class of nucleophiles for halocyclization of alkenes.

EXPERIMENTAL SECTION

Instruments and Materials

All reactions in nonaqueous media were conducted under a positive pressure of dry argon in glassware that had been oven-dried prior to use unless noted otherwise. Anhydrous solutions of reaction mixtures were transferred via an oven-dried syringe or cannula. All solvents were dried prior to use unless noted otherwise. Thin-layer chromatography (TLC) was performed using precoated silica gel plates (EMD Chemical, 60, F254). Flash column chromatography was performed with silica gel (Silicycle, 40-63 μm). Infrared spectra (IR) were obtained on a Bruker Equinox 55 Spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance spectra (NMR) were obtained on a Varian Unity-Inova 400 MHz or 500 MHz recorded in ppm (δ) downfield of TMS (δ = 0) in $CDCl_3$ unless noted otherwise. Signal splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), or multiplet (m), with coupling constants (*J*) in Hertz. High-resolution mass spectra (HRMS) were performed by the Analytical Instrument Center at the School of Pharmacy or Department of Chemistry on an Electron Spray Injection (ESI) mass spectrometer.

General Method for the Preparation of Imides

To a solution of allylic chloride or bromide **10** (3.6 mmol) in DMF (10 mL) was added potassium phthalimide (998.9 mg, 5.4 mmol) and stirred overnight at room temperature. The mixture was then diluted with dichloromethane and the organic layer was washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The imide product was purified by flash column chromatography using hexane and EtOAc as the eluent.

General Method for the Preparation of Hemiaminals

To a solution of the above imide (2 mmol) in methanol (20 mL) was added $NaBH_4$ (148 mg, 4 mmol) in several portions at 0 °C. The reaction was monitored by TLC. After completion, the reaction was quenched with water and diluted with dichloromethane. The organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The hemiaminal product was purified by flash column chromatography using hexane and EtOAc as the eluent.

General Method for the Bromocyclization of Hemiaminals

To a solution of compound **12** or **15** (0.1 mmol) and TsOH (22.83 mg, 0.12 mmol) in chloroform (2 mL) at room temperature was added N-bromosuccinimide (NBS) (21.4 mg, 0.12 mmol). The reaction was stirred at room temperature until the starting material disappeared as indicated by TLC. The reaction was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes).

Method for the Catalytic Asymmetric Bromocyclization of Hemiaminals

To a solution of compound **12a** (0.05 mmol), $(DHQD)_2PHAL$ (7.8 mg, 0.01 mmol), and TsOH (1.9 mg, 0.01 mmol) in chloroform (1 mL) at room temperature was added NBS (21.4 mg, 0.12 mmol). The reaction was stirred at room temperature until the starting material disappeared as indicated by TLC. The reaction was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes).

RESULTS AND DISCUSSION

Recently, significant progress has been made in the area of catalytic asymmetric halocyclization of alkenes,[10–18] in particular, enantioselective halolactonizations.[19–32] A number of reviews have been published in this area.[33–38] The more synthetically versatile enantioselective intermolecular addition of nucleophiles and halogen electrophiles to alkenes, however, remains largely unexplored.[39–41] We recently

Additional Supporting Information may be found in the online version of this article.

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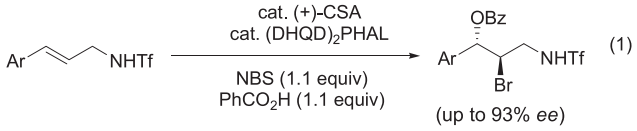
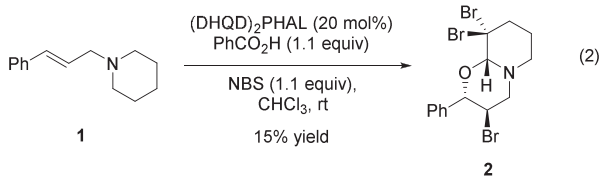
reported the first highly enantioselective intermolecular bromoesterification of alkenes with up to 93% ee (eq. 1.).[42] We found that the enantioselectivity correlated with the acidity of the sulfonamide NH and the most acidic trifluoromethanesulfonamide offered the highest ee. No reaction occurred when the N-H group was replaced by an N-Me group.



We reasoned that the N-H bond in a protonated amine might also direct the intermolecular haloesterification reaction. To our surprise, tertiary amine **1** was oxidized to hemiaminal under acidic conditions and the resulting hemiaminal then served as a nucleophile for the subsequent halocyclization to yield product **2** (eq. 2). The structure of compound **2** was unambiguously assigned by x-ray analysis (Fig. 1).



The mechanism for the formation of bromocyclization product **2** from allylic amine **1** is shown in Scheme 1. Oxidation of allylic amine **1** by NBS followed by elimination of HBr may produce iminium ion **4**, which is in equilibrium with enamine **5**. Bromination of this enamine would then afford iminium ion **6**, which is in equilibrium with enamine **7**. Bromination of enamine **7** would generate iminium **8**, which is in equilibrium with hemiaminal **9**. Bromocyclization of this hemiaminal would yield final product **2**. Apparently, it requires four equivalents of NBS for the conversion of **1** to **2**. The yield of product **2**, however, could not be further improved with additional

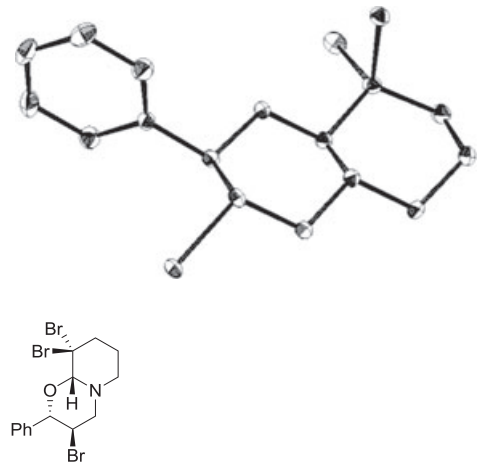
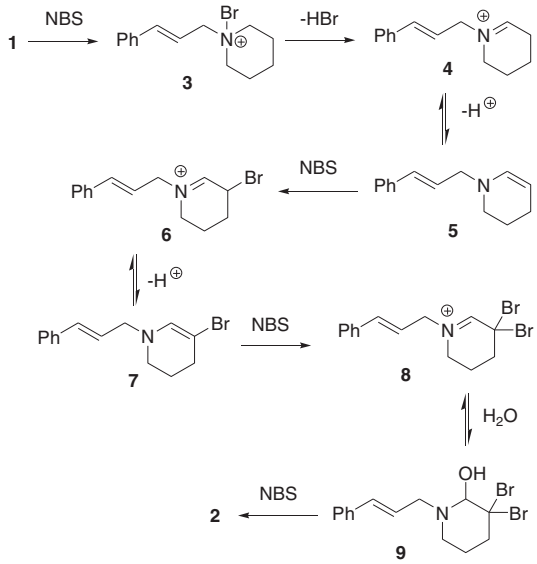


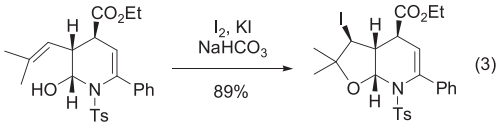
Fig. 1. X-ray structure of compound **2** (CCDC 933536).



Scheme 1. Proposed mechanism for the formation of product **2**.

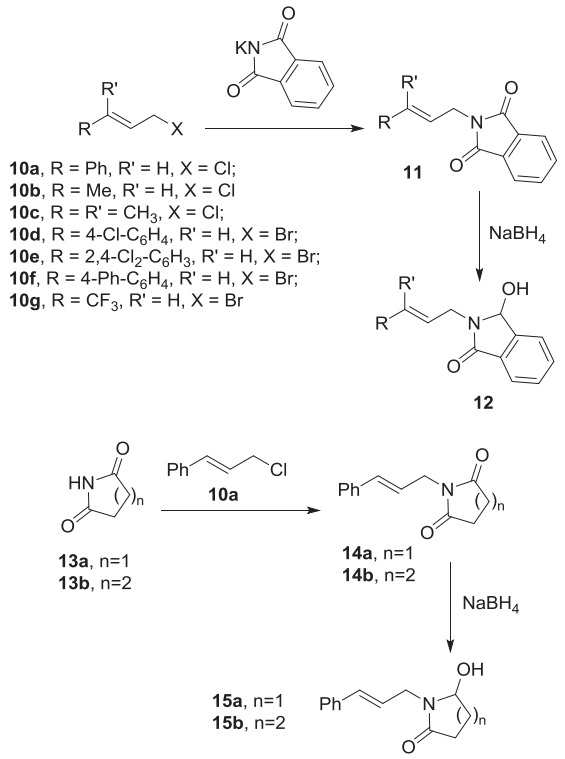
NBS. We also tried to examine the scope of this tandem oxidation-bromocyclization reaction. We observed a complex mixture, however, when *N*,*N*-dimethyl cinnamyl amine or *N*, *N*-diisopropyl cinnamyl amine was treated with NBS under the same conditions.

Aminal is a common structural motif in many natural products and pharmaceutical agents, such as quinocarcin[43,44] and communesins.[45,46] *N*-acylhemiaminal or *N*-acylhemiaminal ether were also found in numerous natural products such as zampanolide,[47,48] echinocandin B,[49] spergualin,[50,51] mycalamides,[52] tallysomycins,[53] and perinadine A.[54] To the best of our knowledge, hemiaminal has not been used as a general nucleophile in halogen-mediated addition reactions for the preparation of hemiaminal ethers. We only found one such example in a report by Chen and coworkers using iodine as the electrophile as shown in eq. 3.[55]



The high diastereoselectivity for the formation of three stereogenic centers in product **2** and the wide presence of *N*-acylhemiaminals or *N*-acylhemiaminal ethers in natural products encouraged us to study *N*-acylhemiaminal as a general nucleophile for stereoselective halocyclizations. *N*-Acylhemiaminals **12a-h** could be easily prepared from the corresponding allylic chlorides or bromides in two steps through a sequence of substitution and reduction as shown in Scheme 2. We also prepared *N*-acylhemiaminals **15a** and **15b** from cinnamyl chloride **10a** and the corresponding 5- or 6-membered cyclic imides.

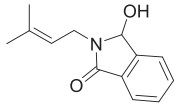
We then treated hemiaminal **12a** with 1.2 equivalents of NBS. We found that the major product was actually imide **17** and the minor product was *N*-acylhemiaminal ether **16a** (eq. 4). The hemiaminal was oxidized quickly by



Scheme 2. Preparation of *N*-acylhemiaminal substrates.

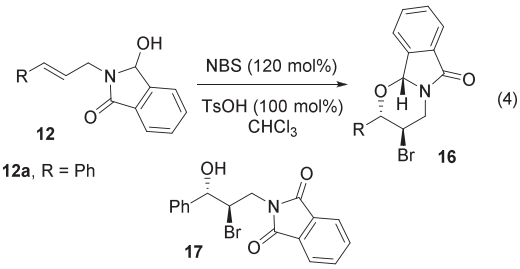
NBS back to imide **11a**, which then underwent intermolecular addition of bromine and water to yield product **17**. No reaction occurred when we treated **12a** with NCS. Interestingly, only imide product was observed when NIS was employed as the halogenation reagent. The selectivity for bromocyclization product **16a** could be improved significantly in the presence of TsOH. An 84% yield of **16a** was isolated under this condition (entry 1, Table 1). Other weaker acids such as benzoic acid led to a complex mixture. The scope of bromocyclization of hemiaminal **12** was then examined (Table 1). The R group can also be an alkyl group (entry 2). No desired product **16c** was observed for substrate **12c** (entry 3). Various substituted aryl groups could be tolerated (entries 4-7).

TABLE 1. Bromocyclization of hemiaminal 12[a]

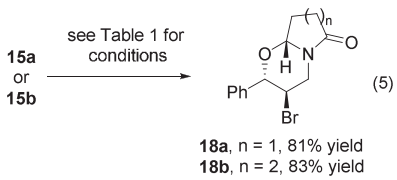
entry	Substrate **12**	Yield[b] (%)
1	**12a**, R = Ph	86
2	**12b**, R = Me	78
	12c	0
3		
4	**12d**, R = 4-Cl-C_6H_4	71
5	**12e**, R = 2,4-Cl_2-C_6H_3	67
6	**12f**, R = 4-Ph-C_6H_4	63
7	**12 g**, R = CF_3	96

[a]Conditions: NBS (120 mol%), TsOH (100 mol%), $CHCl_3$, rt.
[b]Isolated yield.

The structure and relative stereochemistry of product **16e** was unambiguously assigned by x-ray analysis (Fig. 2).



Under the standard conditions, good yields could also be obtained for products **18a** and **18b** (eq. 5).



Finally, we tried to develop the enantioselective bromocyclization of **12a** using chiral catalyst. We first treated hemiaminal **12a** with chiral acid CSA (entry 1, Table 2). Only racemic product was obtained. Addition of catalytic amount of

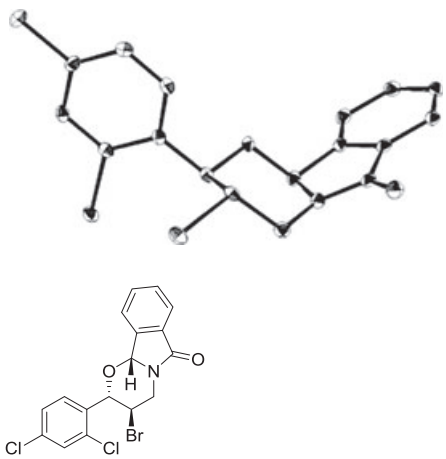


Fig. 2. X-ray structure of compound **16e** (CCDC 933537).

TABLE 2. Conditions for enantioselective bromocyclization of hemiaminal 12a

entry	conditions	Yield (%)	Ee (%)
1	NBS (120 mol%), (+)-CSA (100 mol%), $CHCl_3$	86	0
2	NBS (120 mol%), (+)-CSA (100 mol%), $(DHQD)_2PHAL$ (20 mol%), $CHCl_3$	86	0
3	NBS (120 mol%), (+)-CSA (20 mol%), $(DHQD)_2PHAL$ (20 mol%), $CHCl_3$	47	74
4	NBS (120 mol%), TsOH (20 mol%), $(DHQD)_2PHAL$ (20 mol%), $CHCl_3$	51	64

$(DHQD)_2PHAL$[56–58] to the above system did not induce any enantioselectivity (entry 2). Interestingly, a 74% ee was observed when the amount of acid was reduced to 20 mol% (entry 3). The yield of product **16a**, however, was only 47%. Slightly lower *ee* and similar yield were obtained when achiral acid was employed (entry 4). We were not able to improve the enantioselectivity further by running the reaction in other solvents.

When R is an alkyl group (e.g., substrate **12b**), racemic product **16b** was obtained in a 43% yield. For both substrates **12a** and **12b**, no starting material was left after the completion of the reaction. Instead, a small amount of imide **17** was observed under this condition. We speculate that the equilibration between the two enantiomers of *N*-acylhemiaminal is not very fast under the reaction condition. One enantiomer preferentially underwent bromocyclization while the other one was reluctant to undergo bromocyclization and other pathways including oxidation to imide became competitive. Since only moderate yields and ee's were obtained, the scope of this enantioselective halocyclization was not examined.

CONCLUSION

In summary, we have developed an efficient method for the stereoselective synthesis of *N*-acylhemiaminal ethers **16** and **18** from readily available hemiaminals through bromocyclizations. Three stereogenic centers in these heterocycles were constructed in high diastereoselectivity. Moderate enantioselectivity could also be achieved using dimeric cinchona alkaloid catalysts. Efforts to further improve the enantioselectivity and yields of these halocyclizations are under way in our laboratory.

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