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Enantioselective Bromolactonization of Deactivated Olefinic Acids

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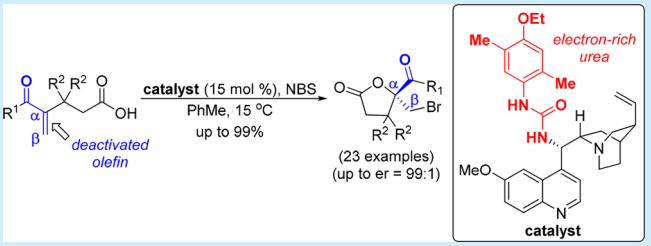
Supporting Information

ABSTRACT: A novel enantioselective bromolactonization of α,β-unsaturated ketones using bifunctional amino-urea catalysts has been developed. The scope of the reaction is evidenced by 23 examples of halolactones bearing various functionalities with up to 99% yield and 99:1 er. Unlike typical urea catalysts that require electron-deficient substituents to enhance the hydrogen bond strength, it is interesting to realize that electron-rich ureas are essential for high enantioselectivity in this case. Moreover, experimental data reveals that the halolactone compounds exhibit considerable anti-inflammatory effects on LPS-induced RAW 264.7 cells.

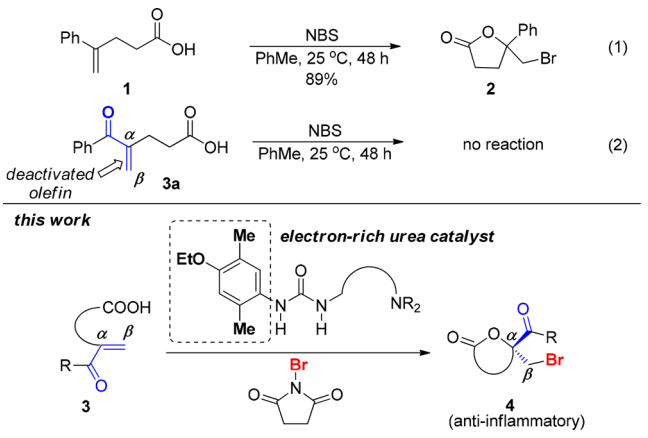


Catalytic enantioselective halocyclization of olefinic substrates is an important approach to achieve various useful heterocyclic building blocks.[1] Various mono- and bifunctional organocatalysts have been widely applied in the asymmetric halocyclization of diverse olefinic substrates.[2−7] Activated or unactivated olefins are typically used in these reactions.

A separated class of substrates is deactivated olefins, which are less studied. Deactivated olefins such as α,β-unsaturated enones are relatively inert toward electrophilic halogenation reactions, attributed to the relatively low reactivity of the electron-deficient olefin as a π-donor in the α,β-unsaturated enone system. For example, olefinic acid **1** was capable of performing the bromolactonization reaction with *N*-bromosuccinimide (NBS) at room temperature, allowing for an efficient synthesis of bromolactone **2** in the absence of catalyst (Scheme 1, eq 1). In contrast, bromolactonization of α,β-unsaturated ketone **3a** under the identical conditions was found to be sluggish (Scheme 1, eq 2).

Sporadic studies were documented, which a metal-catalyzed system can be applied to the halogenation of deactivated olefins. Representative research works on the transition metal-catalyzed haloamidation and related reactions of β-substituted enones reported by Feng et al. have been documented.[6a,8] It has been proposed that the reaction might go through a haliranium intermediate or a Michael addition mechanism.[1f] However, to the best of our knowledge, asymmetric organocatalytic halocyclization of deactivated olefins with nucleophile attacking the α-carbon remains unknown. Herein, we report the halocyclization of deactivated olefinic substrates using a nonclassical urea organocatalyst that bears an electron-donating substituent. The resulting halolactone compounds were found to exhibit significant anti-inflammatory effect on LPS-induced RAW 264.7 cells.

Scheme 1. Bromolactonization of Deactivated Olefinic Acids Catalyzed by Electron-Rich Urea Organocatalyst



At the initial stage of investigation, enone substrate **3a** was examined with toluene as the reaction media. Chiral catalysts including $(DHQ)_2PHAL$ (**5**), BINOL-derived phosphoric acid **6**, and L-proline- and cinchona alkaloid-derived *S*- and *O*-thiocarbamate catalysts **7**−**9** were examined,[1] but the yields were moderate with negligible enantioselectivity. However, cinchona alkaloid derived-ureas **10a**, **11a**, and **12** were found to be effective in promoting the cyclization of **3a**. In particular, urea **10a** gave the desired product **4a** with er 62:38 (Figure 1).

Next, ureas with different substituents were evaluated. Typically, it is believed that urea performs as a dihydrogen-bond catalyst and an electron-withdrawing substituent, which

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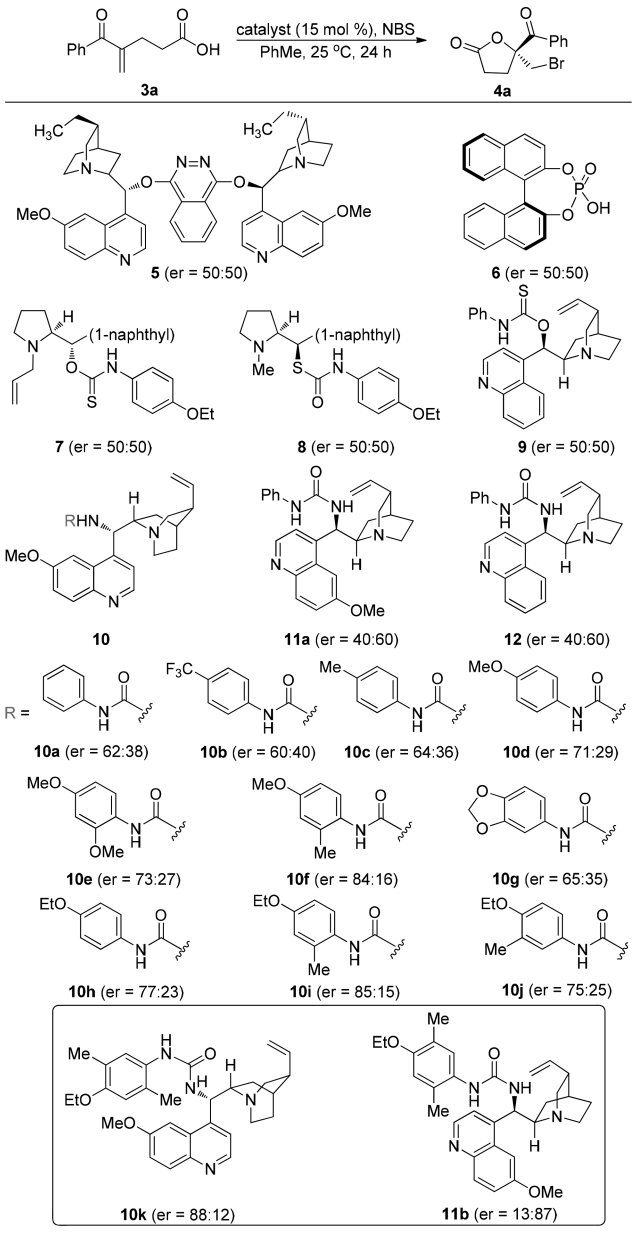
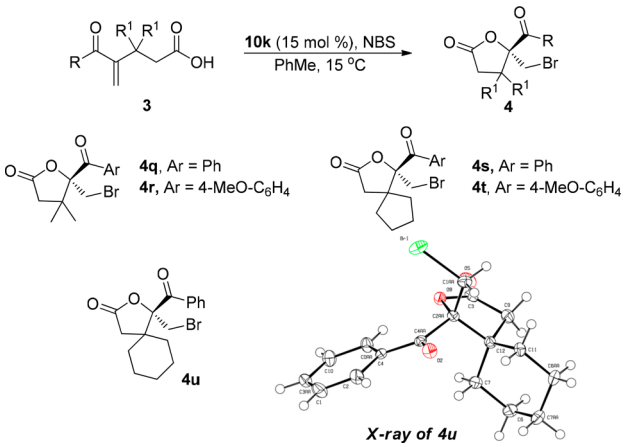


Figure 1. Study on effect of the substituent on the urea catalyst.

should enhance the hydrogen-bond strength and could lead to a better selectivity.[2,9] Unexpectedly, both urea catalysts **10c** and **10d**, which have electron-donating substituents gave better enantioselectivity than that of the relatively electron-deficient urea **10b**. Further examination of different catalysts indicated that the enantioselectivity increased with the electron-donating and steric effects; the enantioselectivity increased significantly with the urea catalyst bearing a 2,4-dimethoxyphenyl (**10e**) or a 2-methyl-4-methoxyphenyl (**10f**) group. However, substitution at the *meta*-position (urea **10g**, **10j**) failed to return a higher enantioselectivity. Changing the 4-methoxy to a 4-ethoxy substitution generally improved the enantioselectivity (**10h** and **10i**). Finally, a 88:12 er was obtained with catalyst **10k**. The antipode of **4a** could be obtained with comparable efficiency when the pseudoenantiomeric quinidine-derived urea **11b** was used. A survey on the halogen source, solvent, and reaction temperature revealed that the use of NBS in toluene at 15 °C was optimal.[10]

With the optimized conditions in hand, the substrate scope was examined. In general, the reactions proceeded with excellent yield and good-to-excellent enantioselectivity (Table 1). The

Table 1. Substrate Scope[a]



entry	4, R	time (h)	yield (%)	er[c]
1	**4a**, C_6H_5	40	96	90:10
2	**4b**, 1-naphthyl	48	87	80:20
3	**4c**, 2-naphthyl	40	99	92:8
4	**4d**, 4-Me-C_6H_4	40	99	90:10
5	**4e**, 3-Me-C_6H_4	42	98	85:15
6	**4f**, 2-Me-C_6H_4	42	97	80:20
7	**4g**, 2,4-Me_2-C_6H_3	42	96	82:18
8	**4h**, 4-MeO-C_6H_4	36	99	94:6
9	**4i**, 4-EtO-C_6H_4	36	99	92:8
10	**4j**, 3-MeO-C_6H_4	40	97	86:14
11	**4k**, 2-MeO-C_6H_4	36	95	59:41
12	**4l**, 4−F-C_6H_4	48	96	90:10
13	**4m**, 4−Cl-C_6H_4	48	98	93:7
14	**4n**, 4−Br-C_6H_4	40	97	93:7
15	**4o**, 4-CF_3−C_6H_4	48	96	86:14
16	**4p**, 2-thienyl	36	99	88:12
17	**4q**	60	98	95:5
18	**4s**	60	99	96:4
19	**4r**	60	99	96:4
20	**4t**	60	99	>99:1
21	**4u**	60	99	>99:1
22[b]	**4h**, 4-MeO-C_6H_4	48	98	94:6
23[c]	***ent*-4h**, 4-MeO-C_6H_4	36	97	7:93
24[d]	**4v**, 4-MeO-C_6H_4	36	98	91:9

[a]Reactions were carried out with substrate **3** (0.2 mmol), catalyst **10k** (0.03 mmol), and NBS (0.26 mmol) in PhMe (8 mL) at 15 °C in the absence of light. The yield was isolated yield, and the er was determined by chiral HPLC. [b]1 mmol scale. [c]Catalyst **11b** was used instead of **10k**. [d]NIS was used instead of NBS. The corresponding iodolactone was obtained instead of bromolactone.

reaction worked well with substrates bearing electron-donating substituents at the *para*-, *meta*-, or *ortho*-positions of the aryl systems (entries 1−10). In particular, the 4-methoxyphenyl substituted substrate **3h** gave the desired product **4h** in er 94:6 (entry 8). Diminished enantioselectivity was encountered for substrate **3k**, presumably due to the presence of a sterically congested substituent (entry 11). The reaction was also found to be compatible with electron-deficient substrates **3l**−**3o** (entries 12−15). Thiophene-containing substrate **3p** gave the corresponding product **4p** smoothly, and the thiophene remained

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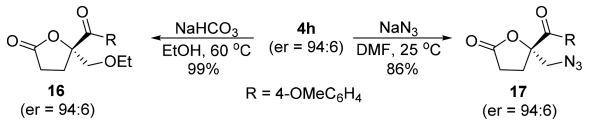
intact (entry 16). Substrates bearing alkyl side-chains including methyls (**3q**, **3r**), cyclopentyl (**3s**, **3t**), and cyclohexyl (**3u**) returned excellent enantioselectivity (entries 17−21), attribute to the crucial role of the Thorpe−Ingold effect.[11] The reaction was found to be readily scalable, and comparable enantioselectivity was obtained (entry 8 vs 22). The antipode of **4** could be obtained by employing the pseudoenantiomeric catalyst **11b** (entry 8 vs 23). Iodolactonization of **3** could be achieved by replacing NBS with *N*-iodosuccinimide (NIS) as the halogen source (entry 24). The absolute configuration of lactone **4** was determined on the basis of an X-ray crystallographic study on a single crystal of **4u**.[10]

The synthetic utility was demonstrated by the transformation using lactone **4h**. As illustrated in Scheme 2, heating **4h** at 60 °C

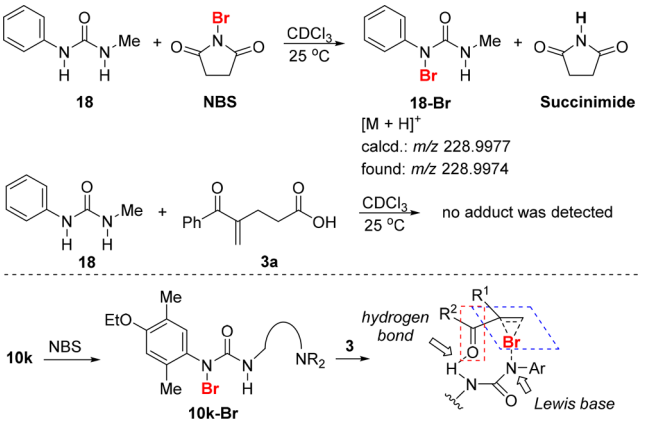
Scheme 2. Synthetic Application



in ethanoic sodium hydrogen carbonate gave the chiral ether derivative **16** in a yield of 99%. However, treatment of **4h** with NaN_3 led to the formation of the azide derivative **17**. More importantly, no erosion of enantioselectivity was observed in both reactions. To investigate the potential use of these products, we evaluated the effects of **4h**, **16**, **17**, and *ent*-**4h** on the production of ROS and NO in LPS-stimulated RAW 264.7 cells. The results show that **4h** considerably reduced the production of ROS and NO, while the effects of **16** and **17** were less significant,[10] indicating that **4h** could be a potent anti-inflammatory agent.[12] Elaboration of these compounds is underway in order to develop potential lead compounds.

Based on the results shown in Figure 1, it appears that the reaction might not go through a classical dihydrogen bond activation mechanism and the bulky, electron-donating substituent in **10k** might offer steric and/or effect(s) in the enantio-determining step. Some control experiments were performed in order to shed light on the mechanistic picture. Upon mixing urea **18** with NBS, in $CDCl_3$, the ^{13}C NMR signals corresponding to NBS and **18** disappeared, and new signals corresponding to succinimide appeared. Concurrently, a white precipitate was formed. HRMS analysis on the white precipitate returned a m/z peak at 228.9974, which might correspond to the species **18-Br** (Scheme 3).[10] However, no observable interaction was detected between urea **18** and enone **3a** on the basis of the NMR study. Although a more detailed study is required to elucidate a clearer mechanistic picture, a plausible reaction mechanism is depicted in Scheme 3 on the basis of the reaction observations. Instead of acting as a dihydrogen-bond catalyst, we postulate that the electron-rich urea **10k** might mainly serve as a Lewis base in activating the electrophilic halogen to give species **10k-Br**.[13] Since efficiency of the electrophilic halogenation was high as reflected by the reaction rate and yield, the olefin moiety in substrate **3** appears to be more electron-rich than expected; this could be a result of inefficient π-conjugation between the carbonyl and the olefinic groups. We suspect that one of the possible transition states might involve dual interactions between the putative species **10k-Br** and the enone moiety in the substrate: (1) the electrophilic Br in **10k-Br** might interact with the olefin to form the bromiranium ion; (2) the N−H group of the urea might hydrogen-bond to the carbonyl oxygen of the

Scheme 3. Proposed Mechanism



enone. These interactions might distort the geometry in such a way that the carbonyl group could not effectively conjugate with the olefin. However, an intensive study is underway in order to gain a better understanding of this new class of catalysts.

In summary, we described a catalytic asymmetric halolactonization of deactivated olefinic acids. A range of keto-lactones were furnished in good-to-excellent enantioselectivity and yield. Instead of classical electron-deficient ureas, electron-rich urea organocatalyst was found to be necessary to achieve high enantioselectivity. Moreover, the lactone compounds were found to be potent anti-inflammatory agents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01125.

Experimental details and spectroscopic and analytical data for new compounds (PDF)

Accession Codes

CCDC 1816471 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(10) The details present in the Supporting Information. CCDC 1816471 contains supplementary crystallographic data for compound **4u**.

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(13) The attempt to generate pure **10k-Br** was unsuccessful. A comprehensive study is underway to elucidate a more detailed mechanism.

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