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Catalytic Asymmetric Intramolecular Bromolactonization of α,β-Unsaturated Ketones

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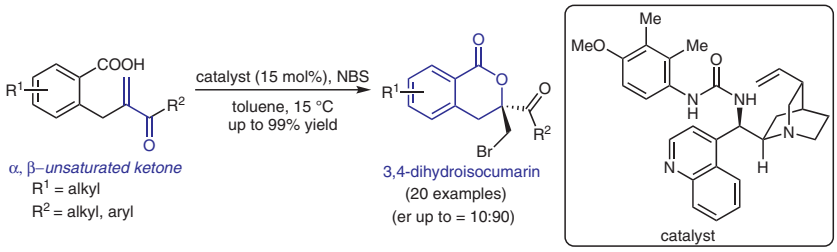

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Abstract Enantioselective bromolactonization by using an amino-urea catalyst to generate the important bromo-containing 3,4-dihydroisocoumarins is described. Excellent yields and good enantioselectivities could be achieved for various 3,4-dihydroisocoumarin compounds.

Key words 3,4-dihydroisocoumarins, bromolactonization, organocatalyst, enantioselectivity, deactivated olefins

Chiral 3,4-dihydroisocoumarins are isolated from a variety of natural sources and possess diverse biological activities.[1] For instance, mullein, a trail pheromone, exhibits antifungal, antimicrobial, and HCV protease-inhibitory activities (Figure 1).[1b] AI-77-B, isolated from a culture broth of *Bacillus pumilus*, possesses gastroprotective and antiulcerogenic properties.[1b,d] Ochratoxin A is one of the most abundant food-containing mycotoxins and shows nephrotoxic, hepatotoxic, carcinogenic, and teratogenic properties.[1e,f] Chiral 3-pentyl-3,4-dihydrocoumarin has significant cytotoxic properties.[1a,g] Methods to access this important building block usually utilize chiral starting materials that can be converted into the desired molecules by multi-step pathways.[2] However, enantioselective catalytic approaches to achieve chiral 3,4-dihydroisocoumarins are still very limited.[3] Therefore, developing useful methods to obtain diverse enantioenriched 3,4-dihydroisocoumarins is highly required.

Catalytic enantioselective halocyclization of olefinic substrates is an important strategy to obtain diverse useful heterocyclic backbones.[4] Various mono- and bifunctional organocatalysts have been widely applied in the asymmetric halocyclization of diverse activated or unactivated olefinic substrates.[3g,5–10] Recently, we developed an enantioselective bromolactonization approach to gain diverse halolactones and isochroman-1,4-diones using organocatalysts (Scheme 1, a and b).[11] Deactivated α,β-unsaturated olefins are used in these reactions. In addition, electron-donating substituents on the urea moiety and the carbamate moiety might offer steric and/or electronic effect(s) in the enantiodetermining step.

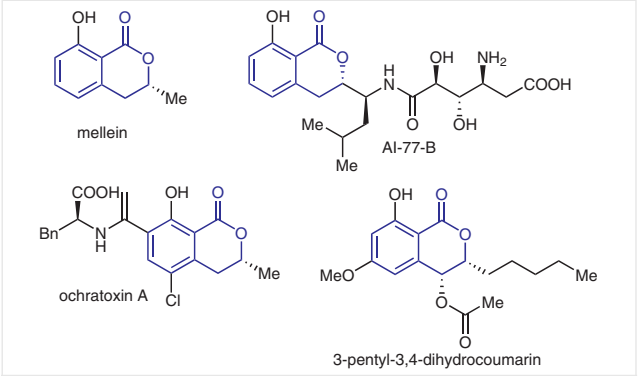

Figure 1 Examples of biologically active chiral 3,4-dihydroisocoumarins

Electrophiles such as α,β-unsaturated ketones serve as one of the most widely used precursors in synthetic reactions.[12] Considering the 3,4-dihydroisocoumarin frameworks, we envisioned an intramolecular bromolactonization protocol. As depicted in Scheme 1, c, α,β-unsaturated carboxylic acid substrate **3** might be converted into the corresponding enantioenriched bromo-substituted 3,4-dihydroisocoumarins **4** in the presence of a halogen source, such as *N*-bromosuccinimide (NBS) and a suitable chiral catalyst. Herein, we describe an organocatalytic process that gives brominated 3,4-dihydroisocoumarins upon bromolactonization of prochiral α,β-unsaturated olefinic precursors.

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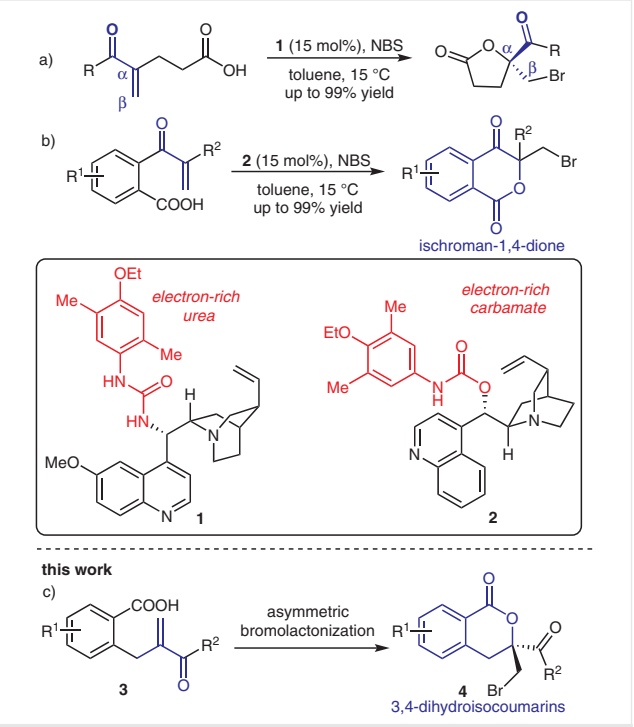
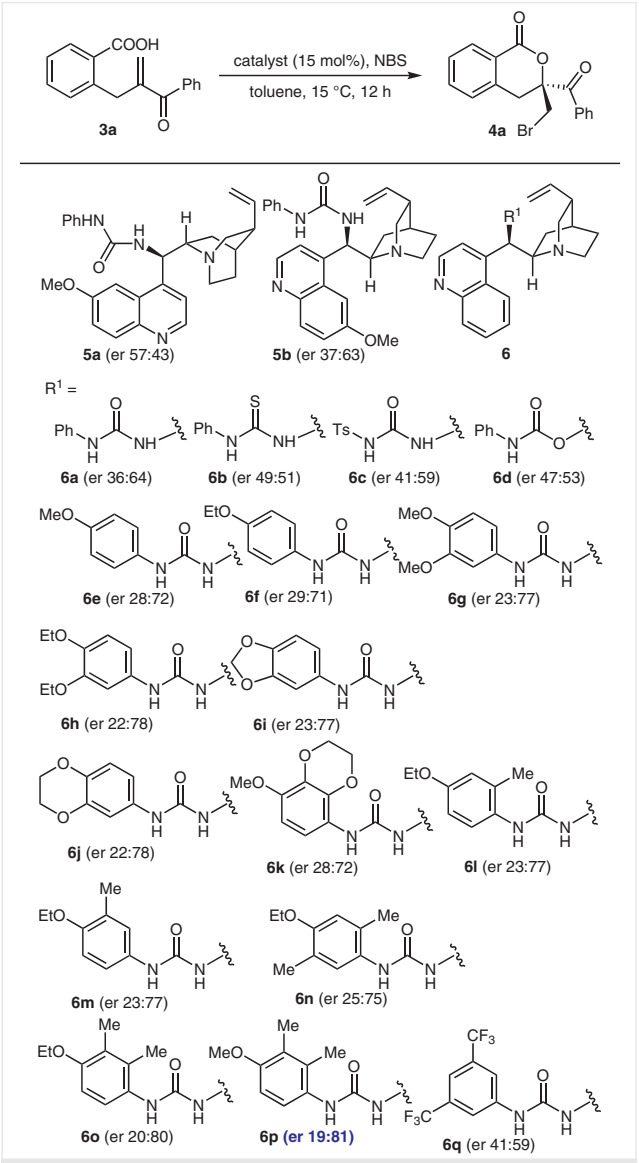
Since an amino-urea catalyst had been beneficial in the previous bromolactonization of α,β-unsaturated carboxylic acids, we tested several cinchona alkaloid-derived urea catalysts. Scheme 2 shows that quinine-derived urea catalyst **5a** led to an enantiomeric ratio (er) of 57:43. Its quasienantiomer, quinidine-derived urea catalyst **5b**, increased the er value. Catalyst **6a**, which bears a cinchonine framework, provided the product with a higher er of 36:64. Other modifications of the urea moiety, such as thio-urea, sulfonylurea, and carbamate (**6b–d**) failed to deliver an acceptable enantioselectivity.



Scheme 1 Bromolactonization of deactivated olefinic acids

Electron-rich substituents, such as methoxyl and ethoxyl groups provided better er values (Scheme 2, 6e and **6f**). The other tested electron-donating systems failed to improve the er value substantially (Scheme 2, 6g–k). Methyl substituents offered a higher enantiomeric induction. The er value increased to 23:77 when additional 2-methyl and 3-methyl substituents were applied (Scheme 2, 6l and **6m**). Further screening led us to use one more methyl group at the benzene ring for the catalyst **6n**, which increased the er value to 25:75. The er value increased to 20:80 when the position of the methyl substituents was fine-tuned (Scheme 2, 6o). Finally, catalyst **6p** gave the desired product with a 19:81 er value. An electron-withdrawing substituent, such as the CF_3 group provided a low enantioselectivity (Scheme 2, 6q).

Subsequent studies focused on optimizing the reaction conditions. As illustrated in Table 1, the enantioselectivity decreased when the reaction was conducted at room temperature (entry 1). The effect of additives, such as BzOH and $NsNH_2$ on the asymmetric bromolactonization of substrate **3a** was detrimental, leading to lower enantioselectivities (Table 1, entries 2–3). Utilization of other solvents, such as Et_2O, EtOAc, CH_2Cl_2, and $CHCl_3$ failed to provide a higher er value (Table 1, entries 4–7). The enantioselectivity increased when the temperature was lowered to 15 °C (Table 1, entry 8). However, further decreasing the temperature to 0 °C proved to be harmful to the enantioselectivity (Table 1,



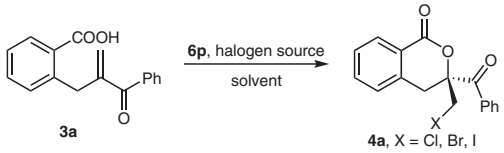
Scheme 2 Study on the effect of the catalyst. [a] Reactions were conducted with substrate **4a** (0.1 mmol), catalyst (0.01 mmol), and NBS (0.12 mmol) in toluene (5 mL) at 15 °C for 12 h in the absence of light. Ts = *p*-tolulenesulfonyl. The er value was determined by chiral HPLC.

entry 9). Use of other bromine sources such as *N*-bromophthalimide (NBP), 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD) showed inferior effects on the enantiomeric induction (Table 1, entries 10–12). The enantioselectivity increased when the catalyst loading was increased to 15 mol% (Table 1, entry 13). The er value decreased when the amount of catalyst was 20 mol% (Table 1, entry 14). It is noteworthy to mention that although the corresponding iodo-substituted 3,4-dihydroisocoumarin product could be obtained in an excellent yield, the enantioselectivity was poor when *N*-iodosuccinimide (NIS) was used instead of NBS (Table 1, entry 15).

1,3-Dichloro-5,5-dimethylhydantoin (DCDMH) was able to perform the chlorolactonization and produced the desired chloro-substituted 3,4-dihydroisocoumarin compound with 83% yield (Table 1, entry 17). Unfortunately, the reaction with *N*-chlorosuccinimide (NCS) was sluggish (Table 1, entry 16). The optimal conditions were found when a toluene/$CHCl_3$ (4:1) solvent system was used and resulted in a 15:85 er value (Table 1, entry 18).

The scope of current bromolactonization reaction is demonstrated by the examples in Scheme 3. First, the effect of substituents at different positions on the phenyl ring (R^2) was investigated. We observed that the enantioselectivity increased when the R^2 group was a 1-naphthyl group (**4b**, er = 14:86). However, the enantioselectivity decreased when a 2-naphthyl group was applied (**4c**, er = 21:79). Moderate enantioselectivities were obtained when 2-, 3- and 4-methyl-substituted phenyl rings were utilized (**4d–f**). We found that the electron-donating 2-methoxyl substituent delivered a high er value of 10:90 along with an excellent yield (**4g**), whereas 3- and 4-methoxyl substituents resulted in lower er values (**4h** and **4i**). The enantioselectivity dropped considerably when a 2-ethoxyl substituent (**4j**, er = 80:20) was used, possibly because of the increased steric hindrance. Electron-withdrawing substituents, such as F, Cl, and CF_3 induced only moderate enantioselectivities (**4k–m**). Good er values could be obtained when the phenyl substituent was located at the *o*-position (**4n**, er = 12:88). The cyclohexyl group delivered a much lower er value (**4o**, er = 36:64), indicating that a π–π interaction is beneficial to the enantioselective induction. A thiophene substituent had a negative effect on the stereocontrol, leading to a low er value (**4p**, er = 25:75). Next, we evaluated the effect of R^1 substituents. We discovered that 2-, 3-, and 4-methyl-substituted phenyl rings resulted in moderate enantioselectivities, though excellent yields were achieved (Scheme 3, 4q, 4r, and **4s**). The reaction was scalable with an equal er value (Scheme 3, 4a, er = 15:85). The absolute configuration of **4b** was determined to be *S* by X-ray crystallographic analysis.[13] The configurations of the other products were assigned by analogy.

Table 1 Optimization of the Reaction Conditions[a]

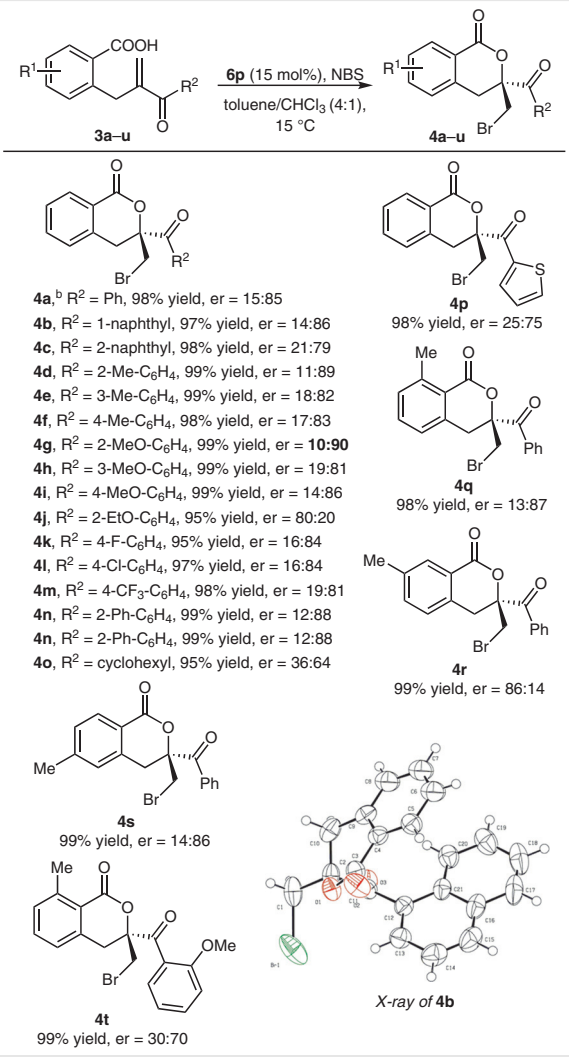


Entry	Halogen source	Conditions	er[b]	Yield (%)[c]
1	NBS	toluene, r.t.	22:78	98
2	NBS	BzOH (1.0 equiv), toluene, r.t.	24:76	96
3	NBS	$NsNH_2$ (1.0 equiv), toluene, r.t.	31:69	97
4	NBS	Et_2O, r.t.	32:68	97
5	NBS	EtOAc, r.t.	29:71	99
6	NBS	CH_2Cl_2, r.t.	36:64	99
7	NBS	$CHCl_3$, r.t.	25:75	99
8	NBS	toluene, 15 °C	19:81	99
9	NBS	toluene, 0 °C	23:79	98
10	NBP	toluene, 15 °C	21:79	97
11	DBDMH	toluene, 15 °C	22:78	98
12	TBCHD	toluene, 15 °C	39:61	96
13[d]	NBS	toluene, 15 °C	18:82	99
14[e]	NBS	toluene, 15 °C	19:81	99
15[f]	NIS	toluene, 15 °C	47:53	99
16	NCS	toluene, 15 °C	–	<5
17[g]	DCDMH	toluene, 15 °C	40:60	83
18[d]	NBS	toluene/$CHCl_3$ (4:1), 15 °C	15:85	99

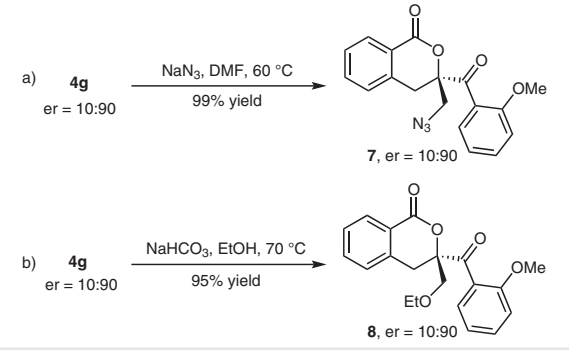
[a] Reactions were carried out with substrate **3a** (0.1 mmol), catalyst **6p** (0.01 mmol), and halogen source (0.12 mmol) in solvent (5.0 mL) in the absence of light. The amount of BzOH or $NsNH_2$ was 1.0 equiv.
[b] The er value was determined by chiral HPLC.
[c] Isolated yield.
[d] The amount of catalyst **6p** was 0.015 mmol.
[e] The amount of catalyst **6p** was 0.02 mmol.
[f] *N*-Iodosuccinimide (NIS) was used as halogen source. The corresponding iodolactone was obtained instead of bromolactone.
[g] 1,3-Dichloro-5,5-dimethylhydantoin (DCDMH) was used as halogen source. The corresponding chlorolactone was obtained instead of bromolactone.

To demonstrate the synthetic utility of this process, further transformations were carried out as shown in Scheme 4. Substitution of Br by using NaN_3 readily gave the desired product **7** in 99% yield without loss of enantiomeric excess (Scheme 4, a). Starting from **4g**, an efficient synthesis of product **8** with high er value was conducted in the presence of $NaHCO_3$ and EtOH (Scheme 4, b).

Because electron-withdrawing amino-urea catalyst **6q** offered a much lower enantioselectivity (Scheme 2), we assumed that a classical di-hydrogen bond activation process might not be involved in this reaction. On the basis of our previous control experiments,[11a] electron-rich urea catalyst **6p** might react with NBS to form species **6p-Br** (Scheme 5), which could be responsible for the enantioselective induc-

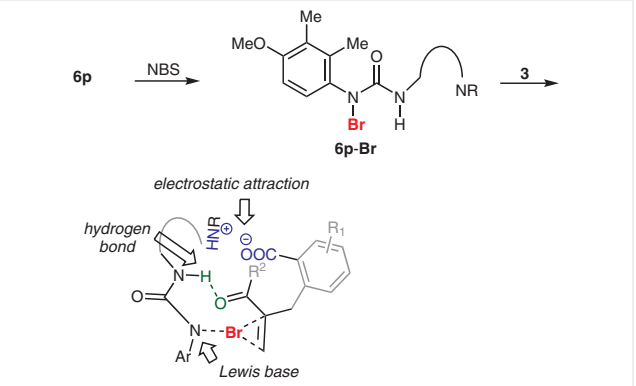


Scheme 3 Substrate scope. [a] Reactions were conducted with substrate **3a** (0.1 mmol), catalyst **6p** (0.015 mmol), and NBS (0.12 mmol) in toluene/$CHCl_3$ (4:1) (5 mL) at 15 °C for 12 h in the absence of light. Isolated yields are given. The er value was determined by chiral HPLC. [b] Reaction was carried out on an 1.0 mmol scale.



Scheme 4 Reactions of **4g**

tion. We suspect that one of the possible transition states might involve several interactions between the putative species **6p-Br** and α,β-unsaturated ketone substrate **3**: (1) the electrophilic Br in **6p-Br** might interact with the alkene to form the bromiranium ion; (2) the N–H group of the urea might form a hydrogen bond with the ketone moiety in **3**; (3) an electrostatic attraction between the basic quinuclidine moiety in **6p** and the carboxylic acid in **3** might be formed. However, the reason why the ketone moiety failed to conjugate with the alkene effectively in this type of α,β-unsaturated substrate remains unclear.



Scheme 5 Proposed mechanism

In summary, we have described an enantioselective protocol to produce various synthetically valuable brominated 3,4-dihydroisocoumarins with excellent yields and moderate to good enantioselectivities.[14] Studies on the reaction mechanism as well as further application of this strategy are ongoing in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611860.

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(13) The details are presented in the Supporting Information. CCDC 1911858 contains supplementary crystallographic data for compound **4b**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(14) General Procedure for Bromolactonization. To a PhMe/$CHCl_3$ (4 mL/1 ml) solution of α,β-unsaturated ketone (0.1 mmol, 1.0 equiv) and catalyst (7.1 mg, 0.15 mmol, 0.15 equiv) at 15°C, in dark under nitrogen was added halogen source (0.13 mmol, 1.3 equiv). The resulting mixture was stirred at 15°C and monitored by TLC. The reaction was quenched with saturated Na_2SO_3 (1 mL) at 15oC and then was warm to room temperature. The solution was diluted with water (3 mL) and extrated with EtOAc, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc=3:1) to yield the corresponding lactone. Supporting Information provides full details and graphical guide.