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Indole-Catalyzed Bromolactonization in Lipophilic Solvent: A Solid–Liquid Phase Transfer Approach

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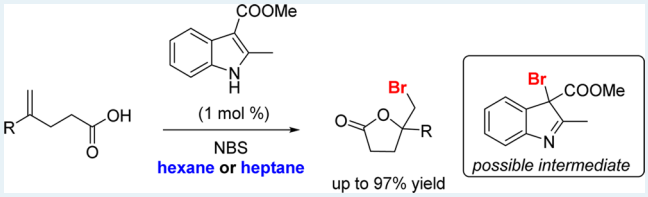
Supporting Information

ABSTRACT: We have developed a novel indole-catalyzed bromolactonization of olefinic acids. The reaction could be conducted in lipophilic solvent through a solid–liquid phase transfer mechanism. This catalytic protocol has been applied to the synthesis of base-sensitive bromolactones.

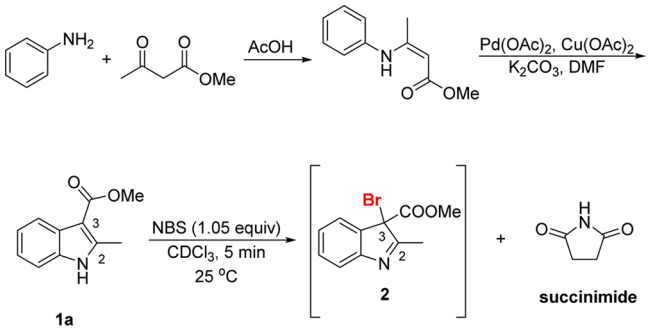


KEYWORDS: *indole, organocatalysis, halolactonization, lactones, phase transfer*

Bromofunctionalization is a key organic transformation. Molecular bromine is an inexpensive brominating source. However, due to its high reactivity, volatility, and corrosiveness, bromine is not an ideal reagent in many modern transformations. Instead, *N*-bromoamide reagents such as *N*-bromosuccinimide (NBS) are commonly employed as they are more stable and easier to handle.[1] Polar solvents such as acetonitrile or DMF can be used to dissolve and activate these polar *N*-bromoamide reagents in order to effect the bromofunctionalization reactions.[2] For relatively nonpolar halogenated solvents such as dichloromethane, promoters are usually required to activate the weakly electrophilic Br in the *N*-bromoamide systems.[3] The Br carrier succinimide is very soluble in both the polar and halogenated solvents, which complicates the purification process particularly for large-scale reactions. Lipophilic solvents (e.g., hexane, heptane) are rarely used as they cannot dissolve the *N*-bromoamide reagents and the promoters. We report herein a new type of bromine activation using a structurally simple indole organocatalyst. This catalytic protocol is applied to the bromolactonization reaction in lipophilic solvents through a solid–liquid phase transfer[4] approach. The reaction condition is mild, which is suitable for base-sensitive compounds. In addition, in lipophilic solvents, the insoluble succinimide can be separated by simple filtration (vide infra).

As part of our interest in the investigation on electrophilic bromofunctionalization of olefins,[5] recently we attempted to use methyl 2-methyl-1*H*-indole-3-carboxylate **1a** as the olefinic partner in bromination reactions. **1a** could easily be prepared using a two-step sequence starting from aniline (Scheme 1).[6] It is well-known that indoles can readily react with halogens to yield the corresponding 3-haloindoles, which are useful building blocks.[7−10] However, an unstable species was obtained when **1a** was treated with *N*-bromosuccinimide (NBS). HRMS data suggested that the newly formed species was a brominated indole **1a**. On the basis of the ^{1}H NMR study on a mixture of **1a** and NBS (1:1) in $CDCl_3$, a new set of signal at the aromatic region was observed, and the original signals of **1a** disappeared.

Scheme 1. Preparation of Indole 1a and the Unstable Species 2



The methylene signal in NBS shifted from 2.98 to 2.70 ppm, which indicates that succinimide was formed.[11] We attempted to isolate the unstable species in pure form with the following procedures: (1) a mixture of NBS and **1a** (1.1:1.0) in CH_2Cl_2 was stirred for 10 min at 25 °C; (2) the solvent was removed under high vacuum at 25 °C to give an orange oil with some white solids (which was found to be succinimide) at the bottom; (3) the orange oil (Figure 1a) was separated for further analysis. The ^{1}H NMR spectrum of the orange oil resembled that of the unstable species. After careful ^{13}C NMR and DEPT 135 studies on the sample, it was found that the C(3) sp^2 signal (104.4 pm) in **1a** shifted to 59.1 ppm, which should correspond to a sp^3 quaternary carbon signal. On the basis of the NMR and HRMS evidence, we speculated that **2** with a Br at C(3) was the unstable species.[11] More importantly, the Br in **2** appeared to be a highly active electrophilic Br source. When subjecting 1,3,5-trimethoxybenzene (**3**) into the $CDCl_3$ solution containing **2**, brominated product **4** was obtained exclusively in 5 min, and indole **1a** was regenerated

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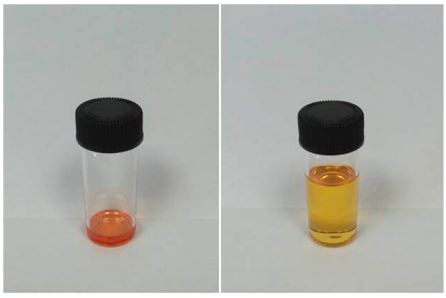


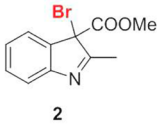
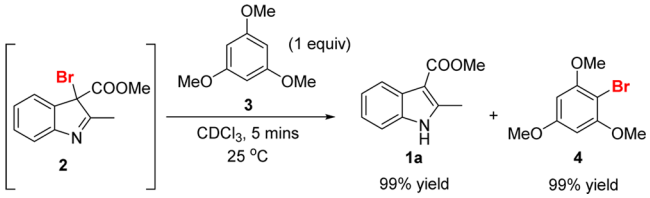


Figure 1. Appearance of **2**: (a) Pure **2**; (b) **2** in hexane.

quantitatively (Scheme 2). Because indole **1a** has low polarity and the unstable species **2** exhibited excellent solubility in

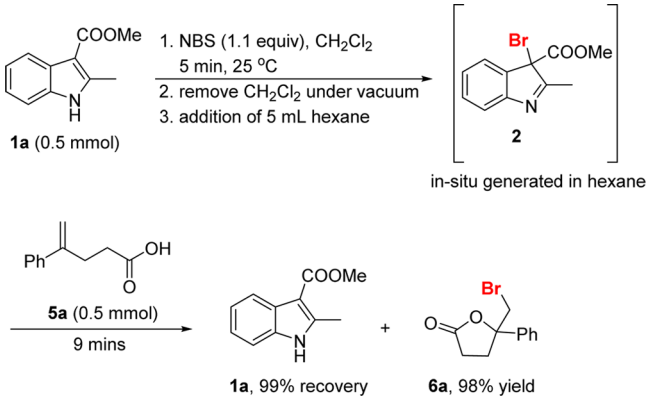
Scheme 2. Bromination of 3 Using Species 2



hexane (Figure 1b), we envisioned that **1a** could potentially be a catalyst for electrophilic bromination in lipophilic media through the novel nonpolar intermediate **2**.[12]

We first examined the reactivity of **2** for the bromolactonization in hexane. **2** was prepared in situ by reacting indole **1a** with NBS in CH_2Cl_2 followed by exchanging the solvent to hexane (Scheme 3). Olefinic acid **5a** was then added and the desired

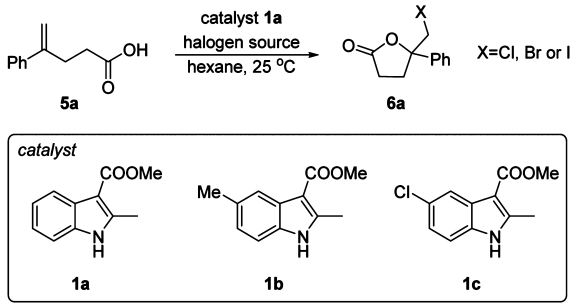
Scheme 3. Bromolactonization of 5a using stoichiometric amount of 2



bromolactone **6a** was obtained quantitatively in 9 min. More importantly, indole **1a** could also be fully recovered, suggesting that **1a** could be a good catalyst for the bromolactonization in hexane.

Indole **1a**-catalyzed bromolactonization of olefinic acid **5a** in hexane at room temperature was examined. As expected, the reaction was sluggish in the absence of catalyst due to the low solubility of NBS (Table 1, entry 1). To our delight, NBS dissolved gradually, and the desired lactone **6a** was furnished in 96% yield in 1 h (entry 2). We further attempted to reduce the catalyst loading and were surprised to find that 1 mol % of

Table 1. Optimization of the Reaction Conditions[a]



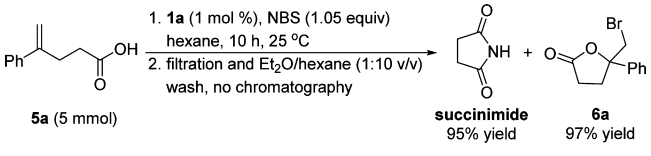
entry	halogen source	**1a** (mol %)	time (h)	yield (%)[b]
1	NBS	0	2	trace
2	NBS	20	1	96
3	NBS	10	1.5	99
4	NBS	5	2	94
5	***NBS***	***1***	***5***	***97***
6	***NBS***	***0.2***	***20***	***90***
7	NBP	1	5	92
8	DBDMH	1	5	94
9	NIS	1	5	97
10	NCS	1	5	0
11[c]	NBS	1	5	96
12[d]	NBS	1	5	88
13[e]	NBS	1	5	95
14[f]	NBS	1	12	80

[a]Reactions were carried out with 4-phenylpent-4-enoic acid (**5a**) (0.5 mmol), catalyst **1a**, and halogen source (0.6 mmol) in hexane (5 mL) at 25 °C. [b]Isolated yield. [c]Indole **1b** was used as the catalyst. [d]Indole **1c** was used as the catalyst. [e]Heptane was used as the solvent. [f]Cyclohexane was used as the solvent. NBS = *N*-bromosuccinimide; NBP = *N*-bromophthalimide; DBDMH = 1,3-dibromo-5,5-dimethylhydantoin; NIS = *N*-iodosuccinimide; NCS = *N*-chlorosuccinimide.

indole catalyst **1** was enough to drive the reaction to completion in 5 h (entries 2−5). Further reduction of the catalyst loading to 0.2 mol % could still result in 90% yield of **6a** in 20 h (entry 6). Other brominating agents such as *N*-bromophthalimide (NBP) and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) could also give high yields using this catalytic protocol (entries 7 and 8). Although *N*-iodosuccinimide (NIS) was found to be suitable in this catalysis to give the iodolactone **6a** (X = I) in excellent yield (entry 9),[13] *N*-chlorosuccinimide (NCS) gave no lactone product (entry 10). Indoles **1b** and **1c**, analogues of **1a**, were investigated, and they gave similar catalytic ability as **1a** (entries 11 and 12). We were also delighted to realize that the reaction worked equally well in heptane and cyclohexane (entries 13 and 14), green alternatives to hexane.[14]

Furthermore, we performed a gram-scale reaction, and we attempted to isolate the product and the Br carrier succinimide without using column chromatography. As shown in Scheme 4,

Scheme 4. Scale-Up Reaction with Recovery of Succinimide under Chromatography-Free Condition



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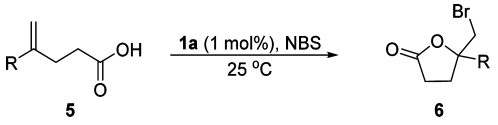
the reaction was first performed under standard conditions. After which, the insoluble succinimide was filtered and washed with small amount of diethyl ether/hexane mixture. The filtrate was concentrated to give lactone **6a** in 97% yield and the purity is >99% based on the ^{1}H NMR study. Pure succinimide (confirmed by ^{1}H NMR) was recovered in 95% yield.

To explore the substrate scope for indole **1a** catalyzed phase transfer reaction, a series of alkenoic acids **5** were investigated using hexane or heptane as the solvent, and the results are summarized in Table 2. In general, the reactions proceeded

Table 2. Indole-Catalyzed Bromolactonization of 5 in Hexane and Heptane[a]



5 **6**

entry	product, R	time (h)	yield in hexane (%)	yield in heptane (%)
1	**6a**, C_6H_5	5	97	97
2	**6b**, 4-Cl-C_6H_4	6	94	95
3[b]	**6c**, 4-CH_3-C_6H_4	9	75	70
4[b]	**6d**, 4-CF_3O-C_6H_4	9	77	71
5[b]	**6e**, 4-NC-C_6H_4	9	81	79
6	**6f**, 2-Cl-C_6H_4	6	91	90
7[b]	**6g**, 3-CH_3O-C_6H_4	9	77	71
8[c]	**6h**, 2-naphthyl	9	90	90
9	**6i**, CH_3	9	95	96
10[b]	**6j**, H	24	89	85

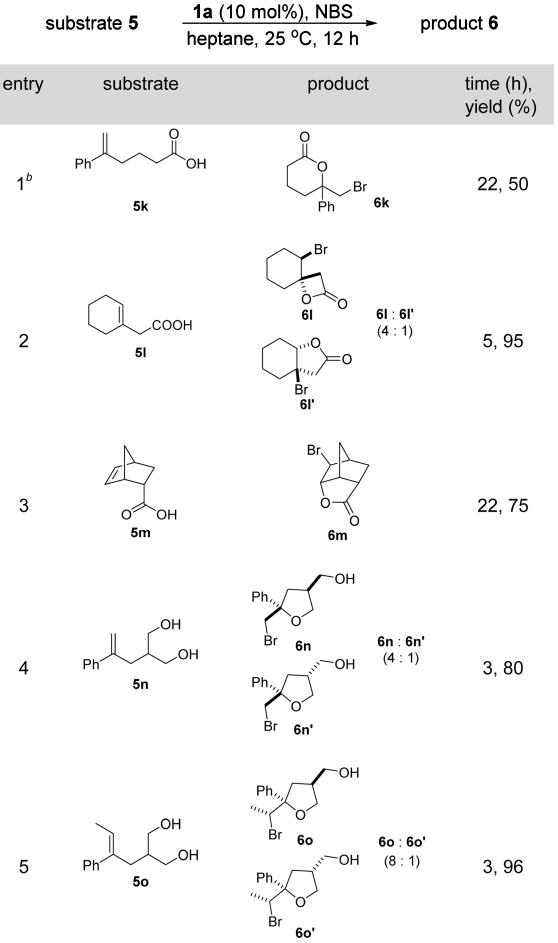
[a]Reactions were conducted with olefinic acid **5** (0.5 mmol), catalyst **1a** (1 mol %), and NBS (0.6 mmol) in hexane or heptane (5 mL) at 25 °C. [b]10 mol % of **1a** was used. [c]20 mol % of **1a** was used.

smoothly, and the desired lactone products **6** were obtained in good to excellent yields. The catalytic protocol was compatible with both electron-rich and electron-poor olefinic substrates. For sterically hindered *ortho*-chloro substrate **5f**, the corresponding lactone **6f** could be obtained in 91% yield. The methyl and unsubstituted substrates **5i** and **5j**, the desired products could still be furnished in high yielding. Other substrates were also examined as shown in Table 3. Although the cyclization of **5k** was relatively sluggish (Table 3, entry 1), the indole-catalyzed bromolactonization of **5l**−**5m** and bromoetherification of **5n**−**5o** proceeded smoothly with good yields and diastereoselectivities (Table 3, entries 2−5).

Besides the reactions that are catalyzed by indole **1a**, as shown above, we also applied this type of catalysis in the synthesis of base-sensitive compound. Previously, our group reported a bromolactonization reaction of olefinic acid **5p** amino-thiocarbamate **8** as the catalyst (Scheme 5).[15] However, a mixture of **6p** and **6p′** with similar polarity was obtained in which **6p** could readily undergo vicinal dehydrobromination to give **6p′** in the presence of base. Indeed, when sodium carbonate, a base commonly used to promote bromolactonization, was employed, a 5:1 mixture of **6p**:**6p′** was obtained. Nonetheless, when the indole catalyst was applied, **6p** was furnished in 90% yield when using heptane as the solvent, and no **6p′** was detected on the basis of the ^{1}H NMR experiment on the crude mixture.

Other substrates (**5q**−**5s**) also worked well under this catalytic protocol to yield the corresponding lactones **6q**−**6s** in excellent yields.

Table 3. Indole-Catalyzed Bromocyclization[a]



[a]Reactions were conducted with olefinic substrate **5** (0.5 mmol), catalyst **1a** (10 mol %), and NBS (0.6 mmol) in heptane (5 mL) at 25 °C. [b]20 mol % of **1a** was used.

On the basis of the experimental results, it appears that indole **1a** might first react with the poorly soluble NBS to give the hexane-soluble brominating species **2** (Scheme 6). The generation of **2** could be facilitated by the formation of the insoluble succinimide byproduct. Subsequent electrophilic bromolactonization of **5** by **2** could furnish lactone **6** together with the regeneration of indole **1a**. It is noteworthy that typically α-carbonyl halide is not an active electrophilic halogen source, and a strong Lewis acid is required to activate the α-carbonyl halide for electrophilic halogenation reactions.[16] For example, a stoichiometric amount of $ZrCl_4$ has been used to activate 2,2-dichloro-1,3-diketone **9** for the electrophilic chlorination.[16c] We speculated that the sole origin of reactivity of **2** could be attributed to the driving force from the rearomatization of the indole (i.e., **2** → **1a**) in the electrophilic bromination process. Although no desired chlorolactone product was obtained when using NCS as the halogen source (Table 1, entry 10), it was found that significant amount of chlorinated indole **11** was isolated when reacting **1a** with NCS (1:1), potentially going through the reactive species **10**.[17]

In summary, we have developed a novel indole-catalyzed bromolactonization using NBS as the stoichiometric brominating agent. The reaction can be conducted in green lipophilic media such as heptane and cyclohexane. The workup process can be facilitated, and the bromine carrier succinimide can be

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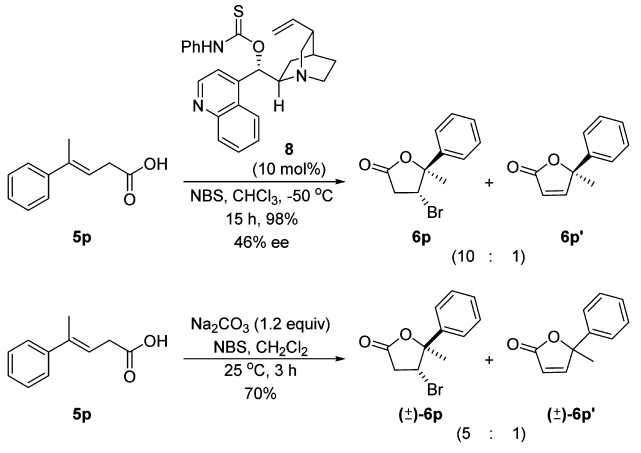
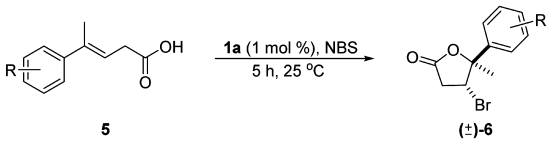
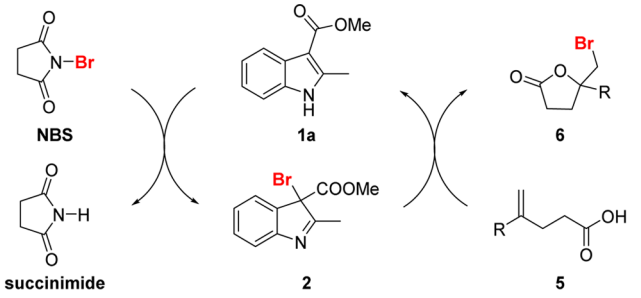
Scheme 5. Indole-Catalyzed Bromolactonization of 5p−5s

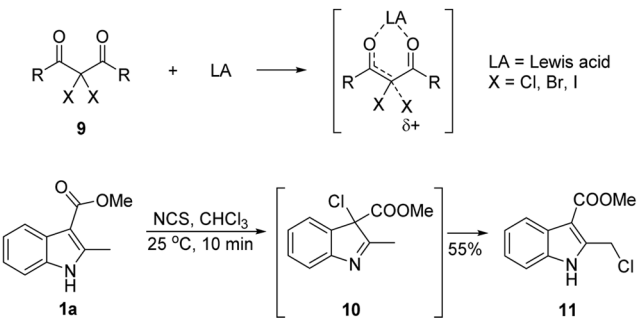




entry	substrate	R	**1a** (mol%)	solvent	yield (%)
1	**5p**	H	1	hexane	87
2	**5p**	H	1	heptane	90
3	**5q**	4-Cl	5	heptane	91
4	**5r**	4-Br	5	heptane	93
5	**5s**	3-MeO	5	heptane	95

Scheme 6. Proposed Catalytic Cycle





recovered by simple filtration. This catalytic protocol can be applied to the synthesis of base-sensitive bromolactones. Mechanistic studies suggest that the indole **2** which contains a Br at the C(3) position might be the active electrophilic brominating species. Further application of this catalytic protocol to other reactions is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01182.

Experimental details of the synthesis and characterization of catalysts and products; copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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