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An unexpected Bromolactamization of Olefinic Amides Using a Three-Component Co-catalyst System

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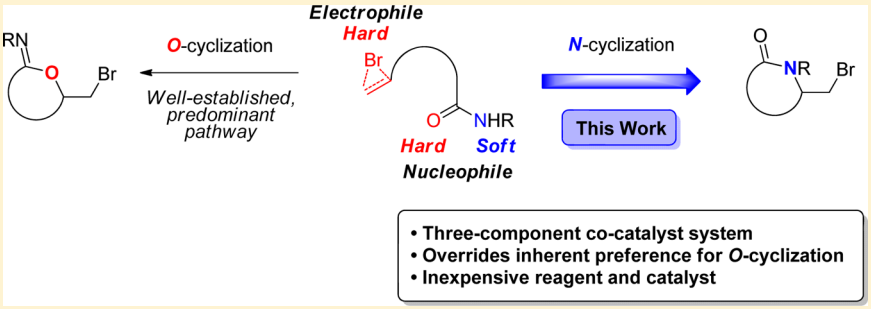
Supporting Information



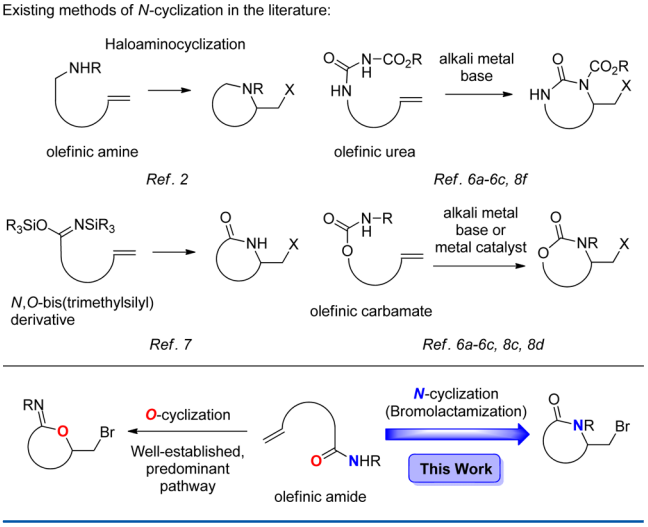
ABSTRACT: Reaction between (*N*,*N*-dimethylamino)pyridine and isocyanate unexpectedly produced a three-component mixture. By using this mixture as an unprecedented three-component catalyst system, a facile and selective bromolactamization of olefinic amides has been developed. The protocol confers enhanced selectivity of *N*- over *O*-cyclization, leading to the formation of a structurally diverse range of lactams including both small and medium ring sizes.

INTRODUCTION

Electrophilic reactions, such as halolactonization, have been the subject of intensive research interest.[1] In recent years, elegant reports on haloaminocyclization reactions have been documented.[2] In haloaminocyclization, olefinic amines, which contain a single nitrogen nucleophile, could undergo ring-closing in the presence of an electrophilic halogen source to afford *N*-heterocyclic products, i.e., pyrrolidines and piperidines. The cyclization of an unactivated olefinic amide, on the other hand, presents formidable challenges. As an olefinic amide contains both oxygen (hard) and nitrogen (soft) nucleophiles in the same system, a key issue is the difficulty to induce *N*-cyclization to give the desired lactam based on the hard/soft acid−base theory (HSAB).[3] Due to the higher electronegativity of oxygen compared to nitrogen in an amide system, *O*-cyclization commonly occurs as the predominant pathway in the halocyclization of olefinic amide substrates, and consequently, there is very little or no *N*-cyclization. In many cases, hydrolysis of the *O*-cyclized products could furnish the corresponding lactones, and this has commonly been employed as a strategy for preparing lactones in various multistep syntheses.[4]

As lactams are prevalent in a variety of natural products and pharmaceuticals,[5] concise and efficient methods to construct lactams will thus be highly valuable from a synthetic viewpoint. Sporadic reports of protocols for electrophilic halocyclization that gave small-ring (e.g., 5- and 6-membered) *N*-cyclized products have been documented (Scheme 1). For example, some cyclizations can be promoted by stoichiometric amounts of alkali metal base.[6] In a report of iodocyclization of *N*,*O*-bis(trimethylsilyl) derivatives, five-membered ring iodolactams can be obtained in good yields, but 2 equiv of moisture-sensitive TMSOTf are required.[7] In many cases, highly specific substrates such as olefinic carbamates or ureas were used to achieve the desired *N*-cyclization.[8] Conversely, a general

Scheme 1. Various Strategies To Achieve *N*-Cyclization



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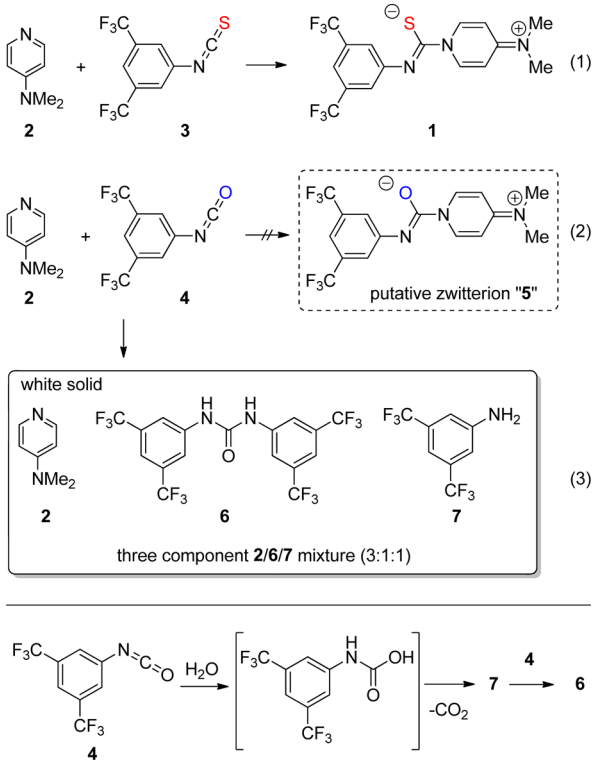
protocol that can effect the direct cyclization of an olefinic amide to give the lactam remains largely elusive. Recently, we reported a carbamate-catalyzed enantioselective bromolactamization process.[9] Building on our recent research effort, we envisage that the development of a more general halolactamization reaction that (1) uses readily available catalysts and reagents and (2) encompasses a broader and more structurally diverse range of substrates would greatly enhance its utility in synthetic chemistry. In addition, there is no reported case on the synthesis of medium-ring size lactams through a catalytic halolactamization process.[10] Herein, we disclose an unexpected result of the use of a three-component catalyst system in the lactamization (*N*-cyclization) of olefinic amides that addresses these gaps in the current literature. While most cocatalyst systems involving two catalytic species have been studied,[11] this report will demonstrate a highly uncommon cooperative organocatalytic protocol using three catalytic species.

RESULTS AND DISCUSSION

Previously, we described the use of the sulfur-based zwitterionic catalyst **1** in the medium-ring lactonization reaction of olefinic acids.[12] The sulfur catalyst **1** could be obtained by the reaction between (*N*,*N*-dimethylamino)pyridine (DMAP, **2**) and aryl isothiocyanate **3** (Scheme 2, eq 1). Our more recent

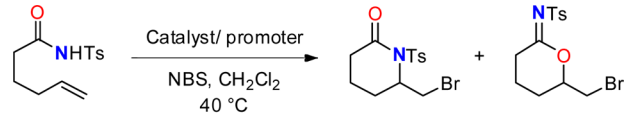
Scheme 2. Synthesis of Catalysts and Proposed Origin of 6 and 7



experiments to obtain the analogous oxygen zwitterion (i.e., the putative zwitterion "**5**") for the halocyclization, however, have led to an intriguing discovery. When DMAP (**2**) was reacted with 3,5-bis(trifluoromethyl)phenyl isocyanate (**4**), a white solid was obtained. Detailed physical analysis revealed that this white solid was not the putative zwitterion "**5**" (Scheme 2, eq 2) but unexpectedly consisted of three components: DMAP (**2**), *N*,*N*′-bis[3,5-(bistrifluoromethyl)-phenyl]urea (**6**), and 3,5-(bistrifluoromethyl)aniline (**7**) in a 3:1:1 ratio (Scheme 2, eq 3). When the individual components were mixed according to the 3:1:1 ratio, the same ^{1}H NMR spectra could be obtained as that of the white solid. On the basis of the ratio, we speculated that the three components were furnished as a result of the rapid hydrolysis of 3,5-bis(trifluoromethyl)phenyl isocyanate (**4**) by moisture[13] to yield the corresponding carbamic acid followed by decarboxylation, which gives aniline **7**. Nucleophilic attack of aniline **7** to another molecule of isocyanate **4** could then yield urea **6**. It is worth mentioning that in the absence of DMAP (**2**) the hydrolysis of **4** to give **7** was sluggish.

More surprisingly, it was realized that the unexpected three-component mixture could catalyze the bromolactamization of olefinic amides. The initial model reaction was performed using olefinic amide **8a** as the substrate and *N*-bromosuccinimide (NBS) as the stoichiometric halogen source. Compound **8a** contains an electron-withdrawing *p*-toluenesulfonyl group which increases the acidity of the amide proton and therefore might aid in *N*-cyclization. The *N*-cyclization and *O*-cyclization selectivity was examined using ^{1}H NMR. Initially, we tested several literature reported protocols that could promote *N*-cyclization. Sodium hydrogen carbonate and triethylamine, which could be used to induce *N*-cyclization of alkenyl urea systems,[8f] as well as *N*,*N*′-bis[3,5-(bistrifluoromethyl)phenyl]-thiourea (**10**),[14] were ineffective in promoting the desired *N*-cyclization of **8a** (Table 1, entries 1−4). Notably, the reaction was also inert toward $CuBr_2$, a promoter used in bromoaminocyclizations[2f] (entry 5) and a combination of $Pd(OAc)_2$/$CuBr_2$ (entry 6), that had been used in the bromo-*N*-cyclization of olefinic carbamates.[8a,b] In the presence of zwitterionic catalyst **1**, a moderate *N*/*O*-selectivity was obtained (Table 1,

Table 1. Catalyst Screening of the Bromolactamization of Substrate Amide 8a[a]



8a 9a 9a'

entry	catalyst/promoter (loading)	time (h)	ratio of **9a**:**9a**′[b]
1	$NaHCO_3$ (1.6 equiv)	0.5	1:10.0
2	Et_3N (5 mol %)	0.5	NR
3	Et_3N (1.6 equiv)	0.5	NR
4	**10**, S=C[NH(3,5-$CF_3C_6H_3$)]$_2$ (5 mol %)	0.5	**9a**′ only
5[c]	$CuBr_2$ (1.0 equiv)	24	NR
6[d]	$Pd(OAc)_2$ (10 mol %)	24	NR
7	**1** (5 mol %)	0.5	1:0.74
8	white solid (**2**/**6**/**7**, 3:1:1) (5 mol %)	0.5	1:0.4
9[e]	white solid (**2**/**6**/**7**, 3:1:1) (5 mol %)	0.5	NR
10[f]	white solid (**2**/**6**/**7**, 3:1:1) (5 mol %)	0.5	1:1.1

[a]Reactions were carried out with olefinic amide **8a** (0.3 mmol), catalyst, and NBS (0.45 mmol) in CH_2Cl_2 (6 mL) at 40 °C in the absence of light. [b]Determined by ^{1}H NMR analysis on the crude product mixture with internal standard. Unless stated otherwise, full consumption of **8a** was achieved. [c]MeCN (6 mL) was used as the solvent. [d]Reaction was carried out with **8a** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), $CuBr_2$ (1.5 mmol), and K_2CO_3 (0.6 mmol) in THF (3 mL) at 25 °C in the absence of light. [e]*N*-Chlorosuccinimide was used as the halogen source. [f]*N*-Iodosuccinimide was used as the halogen source. NR = no reaction.

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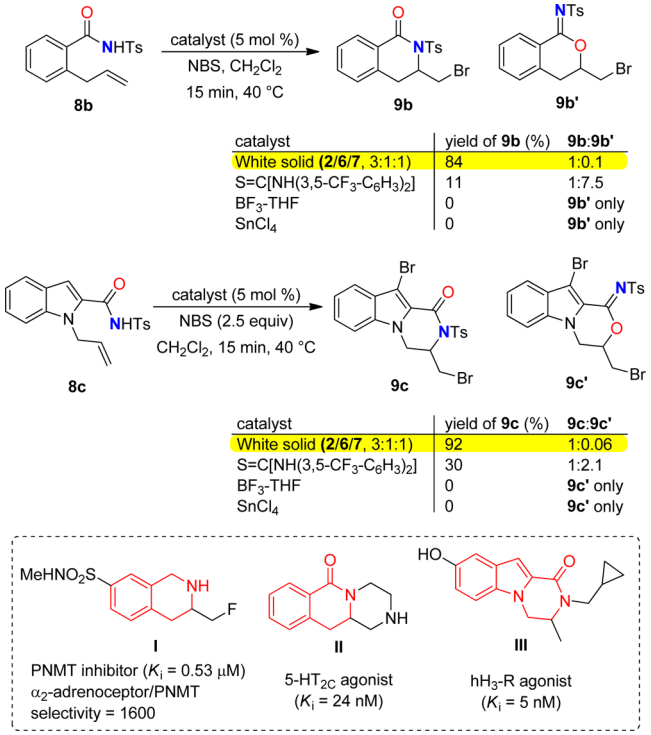
entry 7). When the white solid (**2**/**6**/**7**, 3:1:1) was employed as a catalyst (5 mol %) to the reaction, the selectivity was further enhanced to 1:0.4 in favor of the formation of lactam (Table 1, entry 8) in a short reaction time of 30 min. Interestingly, no reaction was observed when *N*-chlorosuccinimide (NCS) was used, while *N*-iodosuccinimide (NIS) resulted in poorer selectivity (Table 1, entries 9 and 10).

Further experiments demonstrated that the presence of all three components is critical in the catalysis. The *N*-selectivities dropped dramatically when one or two components were removed from the catalyst system.[15] When **2**, **6**, and **7** were individually mixed in a 3:1:1 ratio and used as a reconstituted catalyst system in place of the white solid in the bromolactamization of **8a**, the same *N*/*O*-cyclization ratio could be obtained.[16]

With this promising result, we next directed our efforts toward the synthesis of pharmaceutically important moieties based on the 1,2,3,4-tetrahydroisoquinoline and indole scaffolds (Scheme 3).[17] The synthesis of these scaffolds usually requires

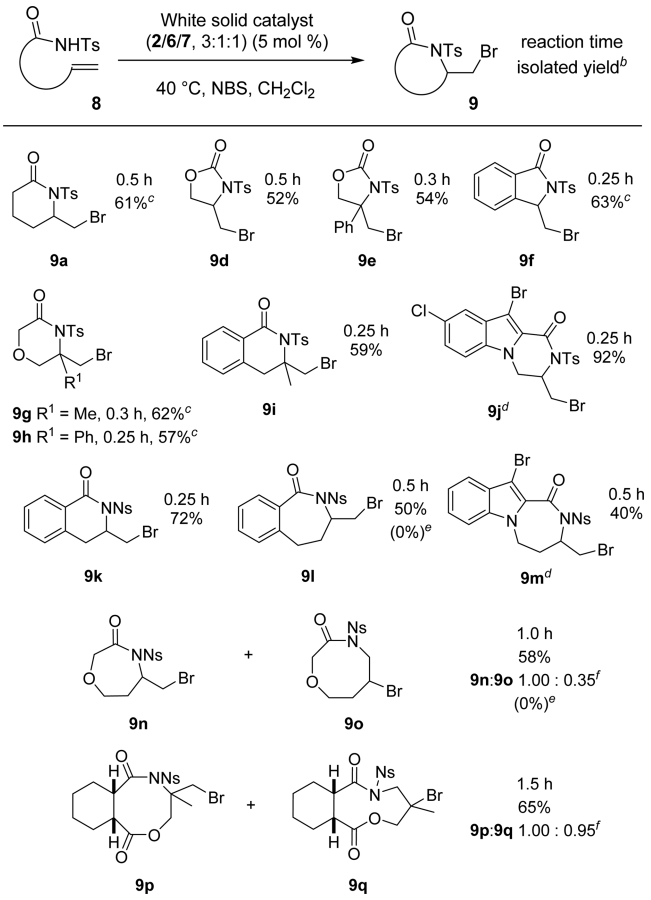
Scheme 3. Cyclization of 8b and 8c



laborious multistep sequences. Nonetheless, cyclization of **8b** under the optimized conditions gave 1-oxo-1,2,3,4-tetrahydroisoquinoline **9b** in 84% yield in just 15 min. The tetrahydroisoquinoline core of **9b** is featured in both the highly selective phenylethanolamine *N*-methyltransferase (PNMT) inhibitor **I**[18] and the serotonin (5-HT_{2c}) receptor agonist **II**.[19] In addition, the skeleton of **III** (a conformationally rigid and potent histamine H_3 inverse agonist which is derived from pitolisant and GSK 189254)[20] could readily be furnished through the cyclization of **8c**, affording **9c** in 92% yield in an equally quick reaction time. In stark contrast, very little or no *N*-cyclized products **9b** and **9c** were formed, and significant amounts of *O*-cyclized products were obtained instead when *N*,*N*′-bis[3,5-(bistrifluoromethyl)phenyl]thiourea or Lewis acids BF_3–THF and $SnCl_4$ were used as catalysts. These observations further attest to the enhanced *N*- over *O*-cyclization selectivity with this novel catalytic protocol. The structures of **9b** and **9c** were confirmed by X-ray crystallographic studies.[15]

The preferential *N*-cyclization also extends to the cyclization of other olefinic amide substrates of varying scaffolds. Table 2

Table 2. Scope of the Bromolactamization of 8[a]



[a]Reactions were carried out with olefinic amide **6a** (0.3 mmol), white solid catalyst (**2**/**6**/**7**, 3:1:1) (0.015 mmol), and NBS (0.45 mmol) in CH_2Cl_2 (6 mL) at 40 °C in the absence of light. [b]Isolated yield by column chromatography. [c]Ca. 25% of *O*-cyclized product was detected as determined by ^{1}H NMR on the crude reaction mixture. [d]2.5 equiv of NBS was used. [e]The parentheses indicate the yield of the bromolactam when the reaction was carried out with **8** (0.3 mmol), $Pd(OAc)_2$ catalyst (0.03 mmol), $CuBr_2$ (1.5 mmol), and K_2CO_3 (0.6 mmol) in THF (3 mL) at 25 °C in the absence of light for 24 h. [f]Determined by ^{1}H NMR.

shows the scope of the halolactamization reaction, where a structurally diverse range of products are displayed. These examples include monocyclic 6-membered lactam (**9a**), cyclic carbamates (**9d** and **9e**), lactams with aromatic scaffolds (**9f**, **9i**, and **9k**), morpholines (**9g** and **9h**), and a piperazine system (**9j**). Notably, medium ring-sized lactams **9l**–**q** could also be furnished by using this catalytic protocol. In the case of formation of **9l** and **9n**/**9o**, attempts were made to synthesize these lactams via palladium catalysis[8a,b] as a comparison, and no reaction was observed. In general, the lactams were achieved with good yields and selectivities.[21] We then explored the possibility of further chemical manipulations on the bromolactam products. Gratifyingly, **9k** could undergo an efficient

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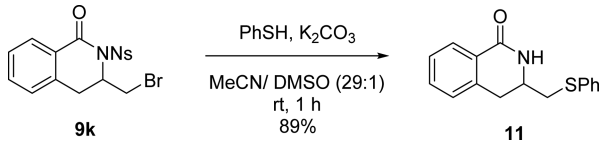
one-pot denosylation and sulfenylation reaction to give lactam **11** in good yield (Scheme 4).

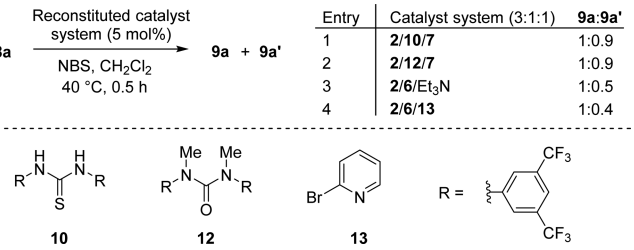
Scheme 4. One-Pot Denosylation and Sulfenylation of 9k



9k **11**

To understand the effect of component variations on the catalysis, we performed further studies using reconstituted catalyst systems (Scheme 5). Thiourea **10**, a sulfur analogue of

Scheme 5. Studies on the Effect of Different Components Using Reconstituted Catalyst Systems



Entry	Catalyst system (3:1:1)	9a:9a'
1	**2/10/7**	1:0.9
2	**2/12/7**	1:0.9
3	**2/6**/Et_3N	1:0.5
4	**2/6/13**	1:0.4

10 **12** **13**

6, gave a lower *N*-selectivity than urea **6** under the same reaction conditions (Scheme 4, entry 1). Modifications to urea **6** were also performed. The *N*,*N*′-dimethylurea **12** returned with lower *N*-cyclized product conversion, suggesting that the N−H might be involved in the reaction mechanism, possibly via a dual hydrogen bonding interaction (entry 2).[22] Interestingly, when the aniline partner was replaced with triethylamine, a similar ratio of **9a**/**9a**′ was obtained. This may suggest that the aromatic and the N−H moieties do not play crucial roles in controlling the selectivity (entry 3). It is noteworthy that triethylamine alone could not promote the bromolactamization (Table 1, entry 2), indicating that the three components might work cooperatively in the reaction (vide infra). A similar selectivity was also obtained when 2-bromopyridine (**13**) was used in place of aniline **7**, which further suggests that the N−H in this weakly basic aniline component is not a dominant factor (entry 4).

In the course of the investigation, we realized that while both urea **6** alone and a mixture of urea **6**/NBS were insoluble in CH_2Cl_2, a DMAP (**2**)/urea **6**/NBS mixture dissolved quickly in CH_2Cl_2 to give a colorless solution. Preliminary studies by ^{1}H NMR indicated that DMAP (**2**), urea **6**, and NBS might interact with one another,[15,23] which could account for these solubility differences. We had also suspected that the three components might react irreversibly to give a new catalytic species in situ. Nonetheless, the possibility was unlikely to happen on the basis of the ^{1}H NMR studies: the chemical shifts and integrations of the individual components perfectly matched with the signals in the 3:1:1 mixture. To further verify this suspicion, a set of careful experiments were performed. The three-component system DMAP (**2**), urea **6**, and aniline **7** were stirred with NBS for 1 h in CH_2Cl_2 at 40 °C. 1,3,5-Trimethoxybenzene (1.2 equiv) was then added to the mixture to capture the electrophilic Br. After that, monobrominated 1,3,5-trimethoxybenzene was obtained quantitatively, and more crucially, all the three components could be recovered. This suggests that the three-component system might work cooperatively through weak interactions (e.g., hydrogen bonding) rather than forming a new species irreversibly.

While a definite mechanism awaits thorough investigation, we could summarize the overall observations on the basis of these studies: (1) aniline **7**, DMAP (**2**), and urea **6**, play unique roles in this catalytic protocol and the three catalytic partners might have a synergetic effect; (2) the relatively weaker base aniline **7** and the relatively stronger base DMAP (**2**) seem to serve different functions in this catalytic protocol.

In summary, a facile and selective bromolactamization of olefinic amides has been developed using an unprecedented three-component catalyst system, with NBS as the stoichiometric brominating agent. *N*-Cyclization preferentially occurs over *O*-cyclization, leading to the formation of a structurally diverse range of lactams including both small and medium-ring sizes.

EXPERIMENTAL SECTION

General Information. All reactions that required anhydrous conditions were carried out via standard procedures under nitrogen atmosphere. Commercially available reagents were used as received. The solvents were dried and purified over a solvent purification system. Thin-layer chromatography (TLC) was performed using precoated silica gel foils. Chromatographic purification was performed on silica gel (0.040−0.063 mm). Infrared spectra were recorded on a FTIR spectrophotometer and reported in wave numbers (cm^{-1}). Melting points were determined on a melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a spectrometer operating at 300 MHz for protons and 75 MHz for carbon nuclei or a spectrometer operating at 500 MHz for protons and 125 MHz for carbon nuclei. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ) in parts per million (multiplicity, coupling constant (Hz), integration). Data for ^{1}H NMR spectra are referenced to the center line of $CDCl_3$ (δ 7.26) as the internal standard. Data for ^{13}C NMR spectra are referenced to the center line of $CDCl_3$ (δ 77.0) as the internal standard. High-resolution mass spectra were obtained on a mass spectrometer in ESI or EI mode using a TOF mass analyzer.

*Preparation of Three-Component Catalyst System **2/6/7** (3:1:1).* (*N*,*N*-Dimethylamino)pyridine (DMAP) (122 mg, 1.0 mmol, 1.0 equiv) was added to a solution of 3,5-bis(trifluoromethyl)phenyl isocyanate (173 μL, 1.0 mmol, 1.0 equiv) in toluene (2 mL) and stirred for 0.5 h. Upon completion, the mixture was filtered to obtain the product as a white solid. The solid was then recrystallized from hot toluene, filtered, and dried under vacuum.

*Three-Component Catalyst System: DMAP (**2**), 1,3-Bis(3,5 bis-(trifluoromethyl)phenyl)urea (**6**), and 3,5-Bis(trifluoromethyl)aniline (**7**) (ca. 3:1:1).* White solid (377.1 mg, quantitative yield). Mp: 75.6−77.3 °C. IR (KBr): 3108, 2939, 1738, 1608, 1385, 1282, 1172, 1123, 995 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): DMAP (**2**) δ 8.21 (d, J = 6.9 Hz, 2H), 6.54 (d, J = 7.0 Hz, 2H), 3.03 (s, 3H); 1,3-bis(3,5-bis(trifluoromethyl)phenyl)urea (**6**) δ 7.87 (s, 1.3 H), 7.46 (s, 0.7 H); 3,5-bis(trifluoromethyl)aniline (**7**) δ 7.19 (s, 0.3 H), 7.02 (s, 0.7 H). ^{13}C NMR (75 MHz, $CDCl_3$): DMAP (**2**) δ 154.6, 148.9, 106.9, 38.9; 1,3-bis(3,5-bis(trifluoromethyl)phenyl)urea (**6**) δ 152.7, 140.8, 132.0 (q, J = 33.3 Hz), 125.0, 121.4, 118.1; 3,5-bis(trifluoromethyl)aniline (**7**) δ 147.7, 132.0 (q, J = 33.3 Hz), 125.2, 113.9, 111.0.

*Representative Procedure for the Preparation of Olefinic Amides **8a** to **8c** and **8f** to **8o**.* The method is based on that in the literature.[8b] 5-Hexenoic acid (119 μL, 1.0 mmol, 1.0 equiv) was added into a solution of 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride, EDCI (250 mg, 1.3 mmol, 1.3 equiv), and DMAP (171 mg, 1.4 mmol, 1.4 equiv) in CH_2Cl_2 (4 mL) at 0 °C. *p*-Toluenesulfonamide, $TsNH_2$ (205 mg, 1.2 mmol, 1.2 equiv), was then added in one portion to the mixture. The mixture was allowed to warm slowly to room temperature and stirred for 24 h. Upon completion, the mixture was diluted with CH_2Cl_2 (6 mL) and washed

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with 1 N HCl solution (10 mL). The organic layer was removed and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. Purification by flash column chromatography (CH_2Cl_2/EtOAc 9:1) gave the amide **8a**.

*Representative Procedure for the Preparation of Olefinic Amides **8d** and **8e**.* The method is based on that in the literature.[24] *p*-Toluenesulfonyl isocyanate (458 μL, 3.0 mmol, 1.5 equiv) was added dropwise to a solution of allyl alcohol (136 μL, 2.0 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was allowed to warm slowly to room temperature and stirred for 0.5 h. Upon completion, the mixture was diluted with water (5 mL). The organic layer was removed and the aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. Purification by flash column chromatography (CH_2Cl_2/EtOAc 9:1) gave the amide **8d**.

*N-Tosylhex-5-enamide (**8a**).*[25] Clear oil (211.9 mg, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (br, 1H), 7.93 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 5.70−5.61 (m, 1H), 4.94−4.89 (m, 2H), 2.42 (s, 3H), 2.26 (t, *J* = 7.6 Hz, 2H), 1.97 (q, *J* = 7.1 Hz, 2H), 1.64 (q, *J* = 7.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 145.0, 137.2, 135.6, 129.5, 128.2, 115.5, 35.3, 32.6, 23.2, 21.6. MS (ESI) $[M - H]^-$: 266.3.

*2-Allyl-N-tosylbenzamide (**8b**).*[25] White solid (299.7 mg, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.16 (br, 1H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 1H), 7.43−7.37 (m, 3H), 7.24 (m, 2H), 5.87−5.79 (m, 1H), 4.94 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.84 (dd, *J* = 17.2, 1.6 Hz, 1H), 3.47 (d, *J* = 6.2 Hz, 2H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 145.0, 139.0, 136.7, 135.3, 132.3, 131.7, 130.8, 129.4, 128.4, 127.8, 126.4, 116.3, 37.1, 21.5. MS (ESI) $[M - H]^-$: 314.3.

*1-Allyl-N-tosyl-1H-indole-2-carboxamide (**8c**).*[25] White solid (339.8 mg, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.60 (br, 1H), 8.09 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.34−7.28 (m, 5H), 7.16−7.11 (m, 1H), 5.93−5.82 (m, 1H), 5.06 (d, *J* = 5.0 Hz, 2H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.84 (d, *J* = 17.1 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8, 145.0, 139.5, 135.7, 133.4, 129.6, 128.3, 127.2, 125.7, 125.7, 122.8, 121.1, 116.3, 110.6, 109.1, 46.8, 21.6. MS (ESI) $[M - H]^-$: 353.3.

*Allyl Tosylcarbamate (**8d**).*[24] Colorless oil (460.3 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.85−5.77 (m, 1H), 5.29−5.21 (m, 2H), 4.56 (d, *J* = 5.7 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.1, 145.1, 135.5, 130.8, 129.6, 128.4, 119.4, 67.3, 21.6. MS (ESI) $[M - H]^-$: 254.1.

*2-Phenylallyl Tosylcarbamate (**8e**).* Colorless oil (575.6 mg, 87% yield). IR (neat): 3246, 3021, 1751, 1427, 1216, 1160, 1090, 759 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.37−7.33 (m, 5H), 7.29 (d, *J* = 8.2 Hz, 2H), 5.55 (s, 1H), 5.33 (s, 1H), 4.99 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.4, 144.9, 141.3, 137.4, 135.4, 129.5, 128.5, 128.2, 128.1, 125.8, 116.3, 67.9, 21.6. HRMS (ESI) calcd for $C_{17}H_{16}NO_4S$ *m*/*z* $[M - H]^-$: 330.0806, found 330.0808.

*N-Tosyl-2-vinylbenzamide (**8f**).* Clear paste (276.9 mg, 92% yield). IR (neat): 3555, 1705, 1409, 1346, 1168, 1051, 737 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.94 (br, 1H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.44−7.39 (m, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.85 (dd, *J* = 17.7, 11.4 Hz, 1H), 5.60 (d, *J* = 17.6 Hz, 1H), 5.30 (d, *J* = 11.4 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.0, 145.1, 137.1, 135.3, 133.7, 131.8, 131.1, 129.5, 128.5, 127.9, 127.7, 127.0, 118.1, 21.6. HRMS (ESI) calcd for $C_{16}H_{16}NO_3S$ *m*/*z* $[M + H]^+$: 302.0845, found 302.0854.

*2-(2-Methylallyloxy)-N-tosylacetamide (**8g**).* Clear oil (267.4 mg, 94% yield). IR (neat): 3656, 3348, 1727, 1418, 1598, 1418, 1160, 856 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.01 (br, 1H), 7.96 (d, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 4.95 (s, 1H), 4.93 (s, 1H), 3.92 (s, 2H), 3.86 (s, 2H), 2.42 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 145.2, 140.0, 135.4, 129.5, 128.4, 114.3, 75.6, 68.6, 21.6, 19.2. HRMS (ESI) calcd for $C_{13}H_{17}NNaO_4S$ *m*/*z* $[M + Na]^+$: 306.0770, found 306.0777.

*2-(2-Phenylallyloxy)-N-tosylacetamide (**8h**).* Yellow oil (282.4 mg, 82% yield). IR (neat): 3344, 3260, 3024, 2920, 1726, 1417, 1350, 1158, 1087 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2, 1.3 Hz, 2H), 7.39−7.34 (m, 3H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.58 (s, 1H), 5.30 (s, 1H), 4.45 (s, 2H), 3.92 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 145.1, 142.5, 137.4, 135.3, 129.4, 129.6, 128.3, 128.2, 125.9, 116.4, 73.6, 68.4, 21.5. HRMS (ESI) calcd for $C_{18}H_{19}NNaO_4S$ *m*/*z* $[M + Na]^+$: 368.0927, found 368.0936.

*2-(2-Methylallyl)-N-tosylbenzamide (**8i**).* Clear paste (287.4 mg, 87% yield). IR (neat): 3257, 3021, 1706, 1411, 1216, 1167 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.9 Hz, 2H), 7.49 (d, *J* = 7.6, 1.3 Hz, 1H), 7.41 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.27 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 4.77 (s, 1H), 4.27 (s, 1H), 3.38 (s, 2H), 2.45 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 166.1, 146.2, 145.1, 137.8, 135.5, 133.2, 131.7, 130.8, 129.5, 128.6, 128.4, 126.9, 112.7, 41.2, 22.9, 21.7. HRMS (ESI) calcd for $C_{18}H_{18}NO_3S$ *m*/*z* $[M - H]^-$ 328.1013, found 328.1011.

*1-Allyl-5-chloro-N-tosyl-1H-indole-2-carboxamide (**8j**).* Yellow solid (350.5 mg, 90% yield). Mp: 185.9−186.9 °C. IR (KBr): 3361, 3264, 1704, 1517, 1457, 1163, 1080, 915 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.32 (br, 1H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 1.3 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.26−7.24 (m, 2H), 7.13 (s, 1H), 5.89−5.82 (m, 1H), 5.05−5.01 (m, 3H), 4.82 (d, *J* = 17.1 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 145.2, 137.8, 135.6, 133.2, 129.8,129.7, 128.5, 126.9, 126.5, 126.4, 121.9, 116.7, 112.0, 108.0, 47.1, 21.7. HRMS (ESI) calcd for $C_{19}H_{18}$ $^{35}ClN_2O_3S$ *m*/*z* $[M + H]^+$: 389.0721, found 389.0731.

*2-Allyl-N-(4-nitrophenylsulfonyl)benzamide (**8k**).* Pale yellow solid (329.0 mg, 95% yield). Mp: 180.7−182.7 °C. IR (KBr): 3166, 3109, 1686, 1527, 1431, 1356, 1312, 1249, 1064, 845 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (br, 1H), 8.43 (d, *J* = 8.3 Hz, 2H), 8.36 (d, *J* = 8.7 Hz, 2H), 7.49−7.46 (m, 2H), 7.33−7.27 (m, 2H), 5.93−5.85 (m, 1H), 5.01 (d, *J* = 10.0 Hz, 1H), 4.81 (d, *J* = 17.3 Hz, 1H), 3.49 (d, *J* = 5.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 150.9, 143.9, 139.1, 137.0, 132.5, 131.8, 131.6, 130.2, 128.0, 126.9, 124.1, 116.8, 37.3. HRMS (ESI) calcd for $C_{16}H_{14}N_2NaO_5S$ *m*/*z* $[M + Na]^+$: 369.0516, found 369.0517.

*2-(But-3-enyl)-N-(4-nitrophenylsulfonyl)benzamide (**8l**).* White solid (306.9 mg, 85% yield).Mp: 124.2−126.8 °C. IR (KBr): 3113, 2866, 1683, 1531, 1179, 1067, 847 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.9 Hz, 2H), 8.32 (d, *J* = 8.9 Hz, 2H),7.43−7.38 (m, 2H), 7.25−7.22 (m, 2H), 5.63−5.55 (m, 1H), 4.87−4.81 (m, 2H), 2.72 (t, *J* = 7.8 Hz, 2H), 2.12 (q, *J* = 7.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 150.8, 143.8, 141.8, 137.1, 132.2, 131.5, 131.2, 130.0, 127.3, 126.3, 124.1, 115.5, 35.3, 32.4. HRMS (ESI) calcd for $C_{17}H_{15}N_2O_5S$ *m*/*z* $[M - H]^-$: 359.0707, found 359.0722.

*1-(But-3-enyl)-N-(4-nitrophenylsulfonyl)-1H-indole-2-carboxamide (**8m**).* Yellow solid (367.1 mg, 92% yield).Mp: 166.4−168.4 °C. IR (KBr): 3289, 1694, 1535, 1421, 1157, 1060, 894 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40−8.34 (m, 4H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.38−7.35 (m, 2H), 7.18−7.15 (m, 2H), 5.69−5.61 (m, 1H), 4.92−4.88 (m, 2H), 4.48 (t, *J* = 6.9 Hz, 2H), 2.43 (q, *J* = 6.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 150.8, 144.1, 139.6, 134.3, 130.0, 126.6, 126.3, 125.5, 124.2, 122.8, 121.5, 117.4, 110.7, 109.0, 44.2, 34.6. HRMS (ESI) calcd for $C_{19}H_{16}N_3O_5S$ *m*/*z* $[M - H]^-$: 398.0816, found 398.0833.

*2-(But-3-enyloxy)-N-(4-nitrophenylsulfonyl)acetamide (**8n**).* Pale yellow solid (251.0 mg, 80% yield). Mp: 94.6−96.2 °C. IR (KBr): 3304, 3285, 3073, 1743, 1532, 1409, 1353, 1188, 939 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.05 (br, 1H), 8.40 (d, *J* = 8.9 Hz, 2H), 8.31 (d, *J* = 8.8 Hz, 2H), 5.84−5.76 (m, 1H), 5.18−5.14 (m, 2H), 3.95 (s, 2H), 3.59 (t, *J* = 6,3 Hz, 2H), 2.38 (q, *J* = 6,3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 150.9, 143.7, 134.1, 129.9, 124.1, 117.9, 71.3, 69.6, 33.6; HRMS (ESI) calcd for $C_{12}H_{13}N_2O_6S$ *m*/*z* $[M - H]^-$: 313.0500, found 313.0503.

*2-Methylallyl 2-(4-nitrophenylsulfonylcarbamoyl)-cyclohexanecarboxylate (**8o**).* Pale yellow solid (365.3 mg, 89% yield). Mp: 116.4−118.2 °C. IR (KBr): 3177, 2953, 2872, 1704, 1529, 1442, 1353, 1308, 1194, 1086 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ

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8.93 (br, 1H), 8.34 (d, J = 8.8 Hz, 2H), 8.25 (d, J = 8.8 Hz, 2H), 4.92−4.78 (m, 2H), 4.41−4.30 (m, 2H), 2.92−2.80 (m, 1H), 2.71−2.64 (m, 1H), 2.14−2.04 (m, 1H), 1.99−1.88 (m, 1H), 1.85−1.70 (m, 2H), 1.66 (s, 3H), 1.62−1.55 (m, 1H), 1.50−1.30 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 172.1, 150.6, 144.0, 139.4, 129.9, 123.9, 112.9, 68.0, 43.9, 43.1, 26.3, 26.0, 23.6, 23.0, 19.3. HRMS (ESI) calcd for $C_{18}H_{21}N_2O_7S$ m/z [M − H]$^-$: 409.1075, found 409.1064.

Representative Procedure for the Bromolactamization of Tosylated Amides. To a solution of amide **8a** (80.2 mg, 0.3 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) in the dark at 40 °C was added white solid catalyst (consisting of DMAP (**2**) (1.83 mg, 0.015 mmol, 0.05 equiv), urea **6** (2.42 mg, 0.005 mmol, 0.017 equiv), aniline **7** (1.15 mg, 0.005 mmol, 0.017 equiv), and *N*-bromosuccinimide (80.1 mg, 0.45 mmol, 1.5 equiv)). The mixture was stirred for 0.5 h at 40 °C and quenched with saturated Na_2SO_3 (6 mL). The solution was diluted with water (4 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography (hexane/EtOAc 9:1 as eluent) to yield the corresponding lactam **9a**.

*6-(Bromomethyl)-1-tosylpiperidin-2-one (**9a**).* Pale yellow solid (63.6 mg, 61% yield). Mp: 130.6−131.9 °C. IR (KBr): 2954, 1696, 1348, 1160, 1088, 803 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 4.81−4.78 (m, 1H), 3.80 (dd, J = 10.1, 3.2 Hz, 1H), 3.52 (t, J = 10.1 Hz, 1H), 2.51−2.32 (m, 3H), 2.44 (s, 3H), 1.88−1.86 (m, 2H), 1.77−1.74 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 145.0, 136.0, 129.3, 128.9, 56.5, 33.3, 32.6, 25.1, 21.6, 15.8. HRMS (ESI) calcd for $C_{13}H_{17}{}^{79}BrNO_3S$ m/z [M + H]$^+$: 346.0107, found 346.0102.

*3-(Bromomethyl)-2-tosyl-3,4-dihydroisoquinolin-1(2H)-one (**9b**).* Pale yellow solid (99.4 mg, 84% yield). Mp: 141.3−142.6 °C. IR (KBr): 3070, 2960, 1692, 1600, 1338, 1245, 737 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 7.8 Hz, 1H), 7.51 (t, J = 6.7 Hz, 1H), 7.34−7.32 (m, 3H), 7.25 (d, J = 7.8 Hz, 1H), 5.17−5.13 (m, 1H), 3.63 (dd, J = 10.1, 3.9 Hz, 1H), 3.49 (d, J = 16.7 Hz, 1H), 3.33 (dd, J = 16.5, 5.5 Hz, 1H), 3.23 (t, J = 10.3 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0, 145.1, 135.9, 135.4, 134.0, 129.4, 128.9, 128.8, 128.5, 127.7, 127.4, 55.4, 30.9, 30.1, 21.6. HRMS (ESI) calcd for $C_{17}H_{17}{}^{79}BrNO_3S$ m/z [M + H]$^+$: 394.0107, found 394.0108.

*10-Bromo-3-(bromomethyl)-2-tosyl-3,4-dihydropyrazino[1,2-a]-indol-1(2H)-one (**9c**).* Pale yellow solid (141.3 mg, 92% yield). Mp: 118.0−120.0 °C. IR (KBr): 3058, 2924, 1689, 1523, 1348, 1166, 1060, 744 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8.2 Hz, 2H), 7.67−7.64 (m, 1H), 7.49−7.45 (m, 1H), 7.37−7.34 (m, 3H), 7.28−7.24 (m, 1H), 5.28 (dd, J = 6.3, 4.4 Hz, 1H), 5.04 (dd, J = 13.3, 4.4 Hz, 1H), 4.23 (d, J = 13.3 Hz, 1H), 3.67 (d, J = 13.3 Hz, 1H), 3.66 (d, J = 10.8 Hz, 1H), 3.27 (dt, J = 11.4, 3.2 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3, 145.6, 135.9, 135.5, 129.7, 129.1, 127.7, 127.6, 122.2, 121.6, 121.6, 110.0, 100.4, 56.0, 41.9, 29.4, 21.7. HRMS (ESI) calcd for $C_{19}H_{17}{}^{79}Br_2N_2O_3S$ m/z [M + H]$^+$: 510.9321, found 510.9323.

*4-(Bromomethyl)-3-tosyloxazolidin-2-one (**9d**).*[8a] Pale yellow solid (52.4 mg, 52% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 8.9 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 4.74−4.69 (m, 1H), 4.44 (t, J = 8.8 Hz, 1H), 4.43 (dd, J = 9.5, 3.8 Hz, 1H), 3.77 (dd, J = 10.7, 2.5 Hz, 1H), 3.71 (dd, J = 10.7, 6.9 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.7, 146.0, 134.3, 129.9, 128.5, 66.9, 56.1, 33.1, 21.7. MS (ESI) [M + Na]$^+$: 354.0.

*4-(Bromomethyl)-4-phenyl-3-tosyloxazolidin-2-one (**9e**).* White solid (66.4 mg, 54% yield). Mp: 158.0−159.4 °C. IR (KBr): 3036, 1621, 1319, 1163, 1077, 966 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 8.2 Hz, 2H), 7.44−7.41 (m, 3H), 7.31−7.28 (m, 4H), 5.03 (d, J = 8.2 Hz, 1H), 4.76 (d, J = 8.2 Hz, 1H), 3.75 (d, J = 12.0 Hz, 1H), 3.71 (d, J = 12.0 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 143.4, 138.2, 136.5, 129.8, 129.3, 129.2, 127.3, 124.3, 88.2, 75.7, 37.3, 21.5. HRMS (ESI) calcd for $C_{17}H_{17}{}^{79}BrNO_4S$ m/z [M + H]$^+$: 410.0056, found 410.0045.

*3-(Bromomethyl)-2-tosylisoindolin-1-one (**9f**).* White solid (72.1 mg, 63% yield).Mp: 204.5−205.2 °C. IR (KBr): 3062, 1726, 1596, 1360, 1172, 1097, 814 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 7.6 Hz, 1H), 7.68 (t, J = 8.2 Hz, 1H), 7.55−7.50 (m, 2H), 7.34 (d, J = 8.2 Hz, 2H), 5.53 (d, J = 2.5 Hz, 1H), 4.28 (dd, J = 11.4, 5.1 Hz, 1H), 4.03 (dd, J = 11.4, 2.5 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 145.4, 143.3, 135.4, 134.2, 130.0, 129.6, 129.6, 128.5, 124.9, 122.5, 60.8, 34.0, 21.7. HRMS (ESI) calcd for $C_{16}H_{15}{}^{79}BrNO_3S$ m/z [M + H]$^+$: 379.9951, found 379.9949.

*5-(Bromomethyl)-5-methyl-4-tosylmorpholin-3-one (**9g**).* White solid (67.8 mg, 62% yield). Mp: 125.5−127.4 °C. IR (KBr): 2978, 1714, 1596, 1464, 1340, 979 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 4.21−4.07 (m, 5H), 3.48 (d, J = 12.7 Hz, 1H), 2.43 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 145.3, 136.6, 129.4, 129.2, 73.0, 69.5, 64.6, 35.2, 21.7, 21.3. HRMS (ESI) calcd for $C_{13}H_{17}{}^{79}BrNO_4S$ m/z [M + H]$^+$: 362.0056, found 362.0043.

*5-(Bromomethyl)-5-phenyl-4-tosylmorpholin-3-one (**9h**).* Yellow solid (72.7 mg, 57% yield). Mp: 174.0−176.0 °C. IR (KBr): 2931, 1725, 1696, 1280, 1175, 1136 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, J = 8.2 Hz, 2H), 7.50−7.48 (m, 2H), 7.41−7.40 (m, 3H), 7.19 (d, J = 8.2 Hz, 2H), 4.71−4.63 (m, 2H), 4,43 (d, J = 12.6 Hz, 1H), 4.38 (d, J = 17.7 Hz, 1H), 4.30 (d, J = 17.1 Hz, 1H), 3.85 (d, J = 12.6 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 145.3, 137.0, 135.6, 130.1, 128.7, 128.6, 128.5, 127.1, 75.3, 69.7, 67.9, 34.9, 21.6. HRMS (ESI) calcd for $C_{18}H_{18}{}^{79}BrNNaO_4S$ m/z [M + Na]$^+$: 446.0032, found 446.0037.

*3-(Bromomethyl)-3-methyl-2-tosyl-3,4-dihydroisoquinolin-1(2H)-one (**9i**).* Pale yellow solid (72.6 mg, 59% yield). Mp: 124.4−126.4 °C. IR (KBr): 2915, 1691, 1605, 1348, 1295, 1170, 809 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.34−7.31 (m, 3H), 7.21 (d, J = 7.6 Hz, 2H), 4.06 (d, J = 10.1 Hz, 1H), 3.94 (d, J = 10.1 Hz, 1H), 3.55 (d, J = 15.8 Hz, 1H), 3.02 (d, J = 15.8 Hz, 1H), 2.43 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 144.4, 138.0, 150.0, 133.8, 129.2, 128.6, 128.5, 128.2, 127.7, 127.3, 65.2, 40.7, 37.8, 25.6, 21.6. HRMS (ESI) calcd for $C_{18}H_{19}{}^{79}BrNO_3S$ m/z [M + H]$^+$: 408.0264, found 408.0271.

*10-Bromo-3-(bromomethyl)-8-chloro-2-tosyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (**9j**).* Yellow solid (150.9 mg, 92% yield). Mp: 254.6−255.9 °C. IR (KBr): 1681, 1522, 1352, 1252, 1167, 1079 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 1.9 Hz, 2H), 7.42−7.40 (m, 1H), 7.37 (d, J = 8.9 Hz, 2H), 7.29 (d, J = 8.9 Hz, 2H), 5.29−5.26 (m, 1H), 5.01 (dd, J = 13.3, 1.3 Hz, 1H), 4.24 (dd, J = 13.3, 3.2 Hz, 1H), 3.69−3.66 (m, 1H), 3.25 (t, J = 10.7 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.1, 145.8, 135.4, 134.3, 129.8, 129.1, 128.5, 128.4, 128.3, 122.8, 121.0, 111.3, 99.4, 55.9, 42.1, 29.3, 21.7. HRMS (ESI) calcd for $C_{19}H_{16}{}^{79}Br_2{}^{35}ClN_2O_3S$ m/z [M + H]$^+$ 544.8931, found 544.8918.

*3-(Bromomethyl)-2-(4-nitrophenylsulfonyl)-3,4-dihydroisoquinolin-1(2H)-one (**9k**).* Pale yellow solid (92.1 mg, 72% yield). Mp: 165.2−167.2 °C. IR (KBr): 3429, 1700, 1605, 1532, 1354, 1173, 1053, 855 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, J = 8.7 Hz, 2H), 8.33 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 7.7 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 5.18−5.15 (m, 1H), 3.62−3.59 (m, 1H), 3.54 (d, J = 20.5 Hz, 1H), 3.40 (dd, J = 16.7, 5.5 Hz, 1H), 3.30−3.26 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 150.7, 144.5, 135.5, 134.7, 130.5, 129.0, 128.7, 128.1, 126.9, 124.0, 55.8, 30.7, 30.5. HRMS (ESI) calcd for $C_{16}H_{13}{}^{79}BrN_2NaO_5S$ m/z [M + Na]$^+$: 446.9621, found 446.9612.

*3-(Bromomethyl)-2-(4-nitrophenylsulfonyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (**9l**).* White solid (65.7 mg, 50% yield). Mp: 181.8−183.9 °C. IR (KBr): 2945, 1704, 1588, 1528, 1339, 1160, 748 cm^{-1}. ^{1}H NMR: ($CDCl_3$, 500 MHz): δ 8.36 (d, J = 8.2 Hz, 2H), 8.25 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.25 (m, 1H), 4.41−4.35 (m, 1H), 3.64−3.60 (m, 1H), 3.57−3.54 (m, 1H), 2.99−2.92 (m, 1H), 2.85−2.81 (m, 1H), 2.35−2.20 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 150.0, 147.4, 139.1, 134.1, 131.2, 129.6, 129.2, 128.6, 127.9, 124.0, 81.3, 33.3, 31.6, 29.1. HRMS (ESI) calcd for $C_{17}H_{16}{}^{79}BrN_2O_5S$ m/z [M + H]$^+$: 438.9958, found 438.9955.

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*11-Bromo-3-(bromomethyl)-2-(4-nitrophenylsulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indol-1-one (**9m**).* Orange solid (67.5 mg, 40% yield). Mp: 199.5−200.7 °C. IR (KBr): 3105, 1687, 1531, 1355, 1178, 1082 cm^{-1}. ^1H NMR: ($CDCl_3$, 500 MHz): δ 8.47 (d, J = 9.5 Hz, 2H), 8.43 (d, J = 8.9 Hz, 2H), 7.69 (d, J = 8.2 Hz, 1H), 7.49−7.46 (m, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.29−7.28 (m, 1H), 4.94 (m, 1H), 4.69−4.65 (m, 1H), 4.58−4.52 (m 1H), 3.10 (m, 1H), 2.70−2.57 (m, 2H), 2.28−2.26 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.7, 144.1, 135.8, 130.9, 127.7, 126.9, 126.2, 124.3, 123.8, 122.1, 121.9, 109.8, 101.1, 40.8, 38.0, 33.1, 32.7. HRMS (ESI) calcd for $C_{19}H_{16}{}^{79}Br_2N_3O_5S$ m/z $[M + H]^+$: 555.9172, found 555.9160.

*5-(Bromomethyl)-4-(4-nitrophenylsulfonyl)-1,4-oxazepan-3-one (**9n**) and 6-Bromo-4-(4-nitrophenylsulfonyl)-1,4-oxazocan-3-one (**9o**) as a Mixture (ca. 1:0.35).* Off-white solid (68.4 mg, 58% yield). Mp: 178.5−180.0 °C. IR (KBr): 1702, 1531, 1352, 1167, 855 cm^{-1}. ^1H NMR: ($CDCl_3$, 500 MHz): **9n** δ 8.37 (d, J = 8.9 Hz, 2H), 8.21 (d, J = 8.9 Hz, 2H), 4.79−4.75 (m, 1H), 4.47−4.35 (m, 2H), 4.14−4.09 (m, 1H), 4.00−3.90 (m, 2H), 7.76 (dd, J = 12.0, 6.9 Hz, 1H), 2.73−2.68 (m, 1H), 2.27−2.20 (m, 1H); **9o** δ 8.37 (d, J = 8.9 Hz, 2H), 8.21 (d, J = 8.8 Hz, 2H), 4.95 (dd, J = 14.5, 10.7 Hz, 1H), 4.63−4.49 (m, 2H), 4.14−4.09 (m, 1H), 4.00−3.90 (m, 2H), 3.73−3.70 (m, 1H), 2.45−2.38 (m, 1H), 2.00−1.97 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4, 172.1, 150.7 (2C), 144.3, 144.0, 130.3, 130.2, 124.0 (2C), 71.6, 70.5, 69.1, 64.9, 56.3, 49.9, 46.8, 46.2, 31.0, 28.5. HRMS (ESI) calcd for $C_{12}H_{13}{}^{79}Br$ N_2NaO_6S m/z $[M + Na]^+$: 414.9570, found 414.9558.

*4-(Bromomethyl)-4-methyl-5-(4-nitrophenylsulfonyl)octahydro-1H-benzo[f][1,4]oxazocine-1,6(3H)-dione (**9p**) and 4-Bromo-4-methyl-6-(4-nitrophenylsulfonyl)decahydrobenzo[g][1,5]-oxazonine-1,7-dione (**9q**) as a Mixture (ca. 1:0.95).* Pale yellow solid (95.8 mg, 65% yield). Mp: 172.2−176.1 °C. IR (KBr): 3480, 3118, 2937, 2860, 1751, 1609, 1528, 1448, 1370, 1311, 1260, 1223, 1190, 1086, 1029, 825, 742 cm^{-1}. ^1H NMR: ($CDCl_3$, 500 MHz): **9p** δ 8.40−8.30 (m, 2H), 8.25−8.20 (m, 2H), 4.24 (d, J = 7.6 Hz, 1H), 3.99 (d, J = 7.6 Hz, 1H), 3.89−3.79 (m, 1H), 3.48−3.40 (m, 1H), 2.94−2.92 (m, 1H), 2.42−2.29 (m, 1H), 2.09−2.03 (m, 1H), 1.80−1.75 (m, 2H), 1.57 (s, 3H), 1.51−1.45 (m, 1H), 1.38−1.31 (m, 1H), 1.05−0.95 (m, 1H), 0.89−0.82 (m, 1H), 0.61 (t, J = 13.2 Hz, 1H); **9q** δ 8.40−8.30 (m, 2H), 8.25−8.20 (m, 2H), 4.55−4.51 (m, 1H), 4.41−4.38 (m, 1H), 3.74−3.67 (m, 1H), 3.48−3.40 (m, 1H), 2.87−2.86 (m, 1H), 2.42−2.29 (m, 1H), 2.09−2.03 (m, 1H), 1.73−1.69 (m, 2H), 1.58 (s, 3H), 1.51−1.45 (m, 1H), 1.38−1.31 (m, 1H), 1.05−0.95 (m, 1H), 0.89−0.82 (m, 1H), 0.73 (t, J = 13.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 173.3, 173.2, 173.1, 150.5 (2C), 144.6, 144.5, 129.5, 129.4, 124.0, 124.0, 84.5, 83.6, 74.1, 72.4, 46.8, 46.4, 41.0, 40.6, 37.5, 35.9, 25.2, 24.4, 24.0, 22.7, 22.6, 22.0, 21.7, 21.4, 21.3, 19.7. HRMS (ESI) calcd for $C_{18}H_{21}{}^{79}BrN_2NaO_7S$ m/z $[M + Na]^+$: 511.0145, found 511.0134.

*Procedure for the One-Pot Denosylation and Sulfenylation of **9k**.*[26] Compound **9k** (42.5 mg, 0.1 mmol) was dissolved in MeCN (1.0 mL), and this solution was added to a suspension of K_2CO_3 (55.3 mg, 0.4 mmol, 4.0 equiv) and PhSH (30.7 μL, 0.3 mmol, 3.0 equiv) in MeCN (1.9 mL) at room temperature under nitrogen atmosphere. DMSO (0.1 mL) was then added, and the reaction mixture was stirred for 1 h. After consumption of the starting material was determined, the reaction was quenched with water (5 mL) and extracted with EtOAc (3 × 4.0 mL). The combined organic extracts were washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography (hexane/EtOAc 4:1, followed by CH_2Cl_2/EtOAc 9:1 as eluent) to yield **11**.

*3-(Phenylthiomethyl)-3,4-dihydroisoquinolin-1(2H)-one (**11**).* Pale yellow solid (23.9 mg, 89% yield). Mp: 134.8−136.6 °C. IR (KBr): 3439, 3171, 3038, 2929, 1658, 1480, 1398, 1330, 1023, 738 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J = 7.6 Hz, 1H), 7.48−7.45 (m, 1H), 7.43−7.42 (m, 2H), 7.39−7.36 (m, 1H), 7.32 (t, J = 7.6 Hz, 2H), 7.29−7.25 (m, 1H), 7.19−7.17 (m, 1H), 6.52 (br, 1H), 3.78−3.73 (m, 1H), 3.23 (dd, J = 13.9, 5.1 Hz, 1H), 3.06 (dd, J = 15.8, 4.4 Hz, 1H), 3.01−2.96 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 137.0, 133.9, 132.4, 131.0, 129.3, 128.5, 128.1, 127.6, 127.3, 127.3, 49.5, 39.5, 33.6. HRMS (ESI) calcd for $C_{16}H_{15}NNaOS$ m/z $[M + Na]^+$: 292.0767, found 292.0775.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02390.

X-ray data of **9b** (CIF)
X-ray data of **9c**(CIF)
^1H and ^{13}C NMR spectra of compounds **8a−o**, **9a−q**, and **11** (PDF)

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Notes

The authors declare no competing financial interest.

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