Asymmetric Catalysis

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Carbamate-Catalyzed Enantioselective Bromolactamization

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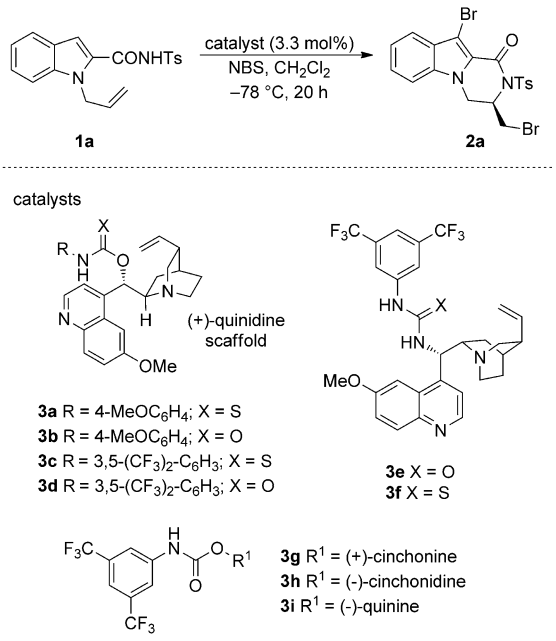
Abstract: *A highly facile, efficient, and enantioselective bromolactamization of olefinic amides was effected by a carbamate catalyst and ethanol additive. The amide substrates underwent N-cyclization predominantly to give a diverse range of enantioenriched bromolactam products containing up to two stereogenic centers.*

Catalytic enantioselective halocyclization of olefinic substrates has been the subject of intensive research interest in recent years.[1] Elegant halocyclization strategies which span various classes of reactions have been documented, including halolactonizations,[2] haloaminocyclizations,[3] and haloetherifications.[4] In contrast, a feasible catalytic and enantioselective halolactamization protocol (i.e. from olefinic amide to lactam) has proven highly elusive to date.[5] A major hurdle lies in the tendency of olefinic amides to undergo O-cyclization, instead to N-cyclization to give the lactam; a consequence of the higher electronegativity of O compared to that of N.[6] Indeed, a handful of enantioselective halo-O-cyclizations of olefinic amides giving oxazine-type products have been reported.[7] Attempts to develop a successful catalytic enantioselective halolactamization protocol thus has to overcome the dual challenge of: 1) overriding the inherent preference for O-cyclization of the amide substrates to give lactams; 2) attaining a suitable catalytic protocol which offers a useful level of enantioselectivity for the lactam products. Herein, we are pleased to report a highly enantioselective bromolactamization promoted by a combination of carbamate catalyst and ethanol additive. This report also represents the first case of an asymmetric reaction catalyzed effectively by a carbamate organocatalyst.[8]

At the initial stage of the investigation, we targeted the cyclization of the olefinic amide **1a**, using *N*-bromosuccinimide (NBS) as the halogen source in CH_2Cl_2 at −78 °C (Table 1). The resultant N-cyclized product **2a** contains a tricyclic amide core which is found in a wide variety of pharmaceutically important molecules.[9] 4-Methoxyphenyl thiocarbamate (**3a**), a well-studied catalyst for asymmetric bromocyclization,[10] gave a modest 33% *ee* (entry 1). The enantioselectivity improved when the catalyst was switched to the carbamate **3b**, the oxygen analogue of **3a** (entry 2). Interestingly, the enantioselectivities were markedly altered when the electron-withdrawing 3,5-bis(trifluoromethyl) substituent was introduced into the N-Ar ring. The thiocarbamate **3c** gave lower enantioselectivity than **3a**, while carbamate **3d** delivered an enhanced 56% *ee* (entries 3 and 4). It is noteworthy that the carbamate catalysts **3b** and **3d** gave higher enantioselectivities than their corresponding thiocarbamate catalysts **3a** and **3c**. This discovery stands in stark contrast to our earlier studies on halolactonization reactions, where the thiocarbamate catalysts gave much higher enantioselectivities than the corresponding carbamates, thus suggesting that the reaction mechanism of carbamate catalysis in halocyclization might be different from that of thiocarbamate.[10] The enantioselectivity did not improve further when either the urea catalyst **3e**, or thiourea **3f**, or carbamate catalysts with other cinchona alkaloid scaffolds

Table 1: Bromolactamization of **1a** using catalysts with various chiral scaffolds.[a]



Entry	Catalyst	Yield [%][b]	*ee* [%]
1	**3a**	90	33
2	**3b**	57	41
3	**3c**	89	19
4	**3d**	88	56
5	**3e**	71	−14
6	**3f**	84	−22
7	**3g**	89	43
8	**3h**	77	−22
9	**3i**	79	−47

[a] Reactions were carried out with olefinic amide **1a** (0.1 mmol), catalyst (0.0033 mmol), NBS (0.24 mmol) in CH_2Cl_2 (2.0 mL). [b] Yield of isolated **2a**. Ts = 4-toluenesulfonyl.

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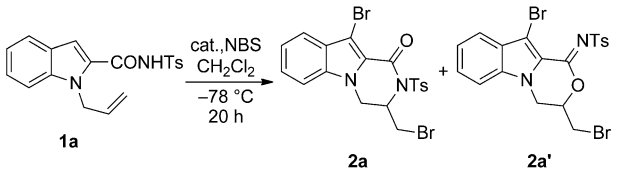
(**3g–i**) were used (entries 5–9). Carbamate catalysts with other N-Ar substituents generally also led to lower enantioselectivities.[11]

It is worth noting that the carbamate catalyst displayed high potency in controlling the N-/O-selectivity when compared to several common catalysts used in halogenation reactions. Intriguingly, **3d** gave exclusively the N-cyclized product **2a** (Table 2, entry 1). In sharp contrast, the N-/O-selectivity was much poorer when other common catalysts for bromocyclization such as Lewis-basic PPh_3 and PPh_3S were used (entries 2 and 3). When the Lewis-acidic catalyst BF_3-THF was employed, the O-cyclized product **2a′** was formed exclusively (entry 4).

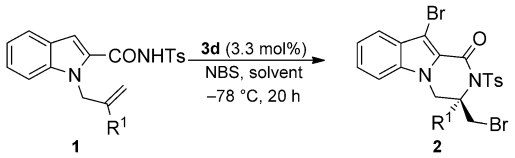
Table 2: Reaction of **1a** with NBS using various catalysts.[a]



Entry	Catalyst	**2a**/**2a′**[b]
1	**3d**	100:0
2	PPh_3	60:40
3	Ph_3PS	60:40
4	BF_3-THF	0:100

[a] Reactions were carried out with olefinic amide **1a** (0.1 mmol), catalyst (0.0033 mmol), NBS (0.24 mmol) in CH_2Cl_2 (2.0 mL). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture upon completion of reaction. THF = tetrahydrofuran.

Table 3: Optimization of the **3d**-catalyzed bromolactamization reaction.[a]

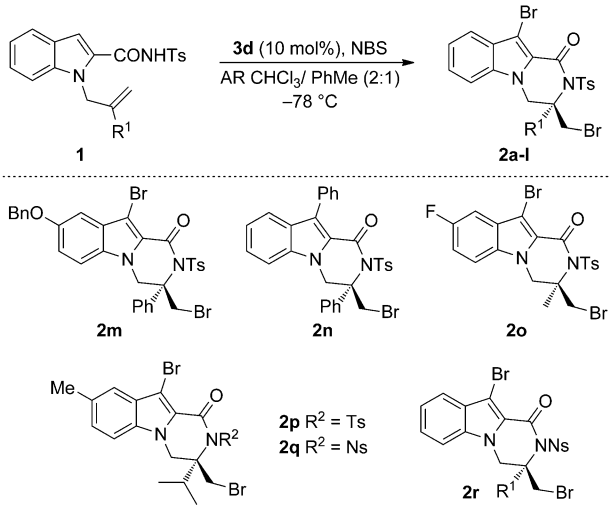


Entry	R^1	Solvent	Yield [%]	*ee* [%]
1	H	CH_2Cl_2	88	56
2[b]	H	AR $CHCl_3$	91	63
3	H	AR $CHCl_3$/PhMe (3:1)	92	68
4	H	HPLC $CHCl_3$/PhMe (3:1)	8	46
5[c]	H	AR $CHCl_3$/PhMe (3:1)	14	50
6[d]	H	AR $CHCl_3$/PhMe (3:1)	11	50
7[e]	H	HPLC $CHCl_3$/PhMe (3:1)	89	68
8	H	AR $CHCl_3$/PhMe (1:1)	93	70
9[f]	Ph	AR $CHCl_3$/PhMe (1:1)	44	85
10[f,g]	Ph	AR $CHCl_3$/PhMe (1:1)	74	86
11[g,h]	Ph	AR $CHCl_3$/PhMe (2:1)	89	94

[a] Reactions were carried out with olefinic amide **1** (0.1 mmol), catalyst (0.0033 mmol), NBS (0.24 mmol) in solvent (2.0 mL). [b] The reaction was conducted at −62 °C. [c] The $CHCl_3$ was treated with microwave-dried 5 Å molecular sieves before use. [d] The $CHCl_3$ was passed through activated neutral Al_2O_3 before use. [e] 15 μL EtOH added. [f] Reaction time was 42 h. [g] 10 mol% **3d** was used. [h] Total amount of solvent was 3 mL and reaction time was 18 h. AR = analytical reagent grade, HPLC = high-performance liquid chromatography grade.

Investigation into other reaction parameters followed and Table 3 summarizes the results obtained. Analytical reagent grade (AR) $CHCl_3$ based solvent blends delivered enhancements to the enantioselectivity (entries 2 and 3). In an unexpected twist, replacing AR grade $CHCl_3$ with high-performance liquid chromatography (HPLC) grade $CHCl_3$ resulted in deterioration in both the reaction rate and the *ee* value (entry 4). After extensive investigations, we suspected that the key to this difference might lie in the EtOH additive (0.6–1.0% v/v) present in AR grade $CHCl_3$. To confirm our suspicion, the EtOH additive was removed by filtering the AR grade $CHCl_3$ through a column of activated molecular sieves or alumina, and the rate and enantioselectivity were found to be low (entries 5 and 6). The yield and *ee* value were restored when 1.0% v/v EtOH was added to the HPLC grade $CHCl_3$ (entry 7), thus indicating the crucial role played by the EtOH additive in mediating the reaction.[12]

Table 4: Substrate scope of bromolactamization of **1** catalyzed by **3d**.[a]



Entry	**2**	R^1	*t* [h]	Yield [%]	*ee* [%]
1	**2a**	H	18	94	68
2	**2b**	Ph	18	89	94
3[b]	*ent*-**2b**	Ph	18	80	−92
4	**2c**	3-$MeOC_6H_4$	22	79	91
5	**2d**	4-MeC_6H_4	20	86	93
6	**2e**	4-vinyl-C_6H_4	45	62	90
7[c]	**2f**	4-$CF_3C_6H_4$	42	82	86
8[c]	**2g**	4-ClC_6H_4	22	92	90
9	**2h**	Me	18	93	90
10	**2i**	*i*Pr	19	92	95
11	**2j**	*t*Bu	48	81	97
12	**2k**	cyclopentyl	18	95	93
13	**2l**	cyclohexyl	18	98	96
14	**2m**	–	18	89	91
15[d]	**2n**	–	42	72	86
16	**2o**	–	18	83	90
17	**2p**	–	19	80	94
18	**2q**	–	19	79	94
19	**2r**	cyclohexyl	18	96	97

[a] Reactions were carried out with olefinic amide **2** (0.1 mmol), **3d** (0.01 mmol), NBS (0.24 mmol) in 2:1 AR grade $CHCl_3$/PhMe (3.0 mL). [b] **3i** (0.01 mmol) was used as the catalyst. [c] The reaction was conducted at −50 °C. [d] 1.2 mmol NBS was used. Ns = 4-nitrobenzenesulfonyl.

This catalytic protocol could also be applied to the bulkier phenyl-substituted substrate **1b** after fine-tuning the reaction conditions, and delivered the product **2b** in 89% yield and 94% *ee* (entries 8–11).

The scope of the bromolactamization was probed and the product diversity is laid out in Table 4. Notably, a switch of catalyst from **3d** to its pseudoenantiomeric form **3i** furnished the antipode of bromolactam **2b** in excellent enantioselectivity of 92% *ee* (entry 3). The reaction proceeded smoothly with electron-rich aryl substituents (entries 4–6). The high *ee* value was maintained even with the inclusion of a vinyl substituent (entry 6). In contrast, substrates with electron-deficient aryl substituents required a relatively higher temperature of −50°C to attain an appreciable reaction rate, albeit with modestly lower enantioselectivities (entries 7 and 8). Alkyl substituents were exceptionally well-tolerated (entries 9–13). Good enantioselectivities were also obtained for substrates with indole ring substituents (entries 14–17). When the Ts group at the amide functionality was replaced with a 4-nitrobenzenesulfonyl (Ns) group (i.e. substrates **1q** and **1r**), the corresponding lactam products **2q** and **2r** could still be obtained with high *ee* values (entries 18 and 19).

In addition to the 1,1-disubstituted alkene substrates in Table 4, the current protocol could be readily adapted to the bromolactamization of *trans*-1,2-disubstituted olefinic amides with little or no change to the reaction conditions (Table 5). The reaction resulted in the formation of bromolactams with two stereogenic centers with excellent diastereoselectivities (entries 1–4). The absolute configurations of **2h** and **5b** (Figure 1) were determined by X-ray crystallographic studies[13] and the stereochemistry of all the other bromolactams **2** and **5** were assigned by analogy. Following the success of the reaction with various disubstituted olefins, we attempted to cyclize the more sterically hindered, trisubstituted olefinic amide **6** as an added challenge (Scheme 1). To our delight, the lactam **7** was furnished in 91% *ee* under the optimized reaction conditions.

The usefulness of the current protocol in medicinal chemistry applications is illustrated in Scheme 2. Cyclization

Table 5: Bromolactamization of trans-1,2-disubstituted olefinic amide **4**.[a]

Entry	5	R^1	Yield [%]	*ee* [%]
1	**5a**	Me	72	91
2	**5b**	Et	97	92
3[b]	**5c**	Pr	88	90
4[b]	**5d**	C_5H_{11}	90	88

[a] Reactions were carried out with olefinic amide **4** (0.1 mmol), **3d** (0.01 mmol), NBS (0.24 mmol) in 2:1 AR grade $CHCl_3$/PhMe (3.0 mL). [b] 3:1 AR grade $CHCl_3$/PhMe (3.0 mL) was used as the solvent combination.

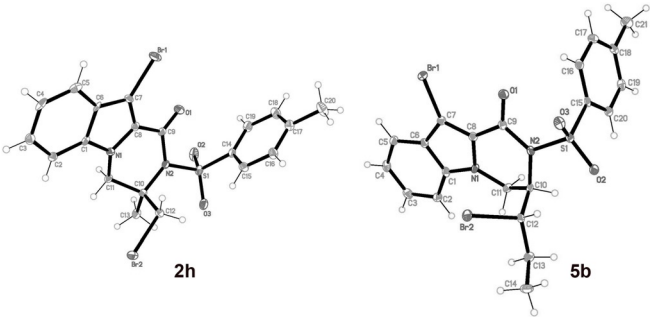
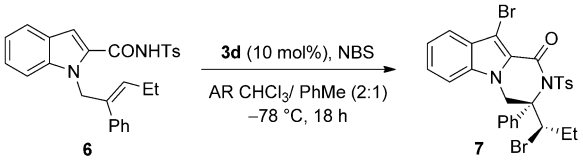
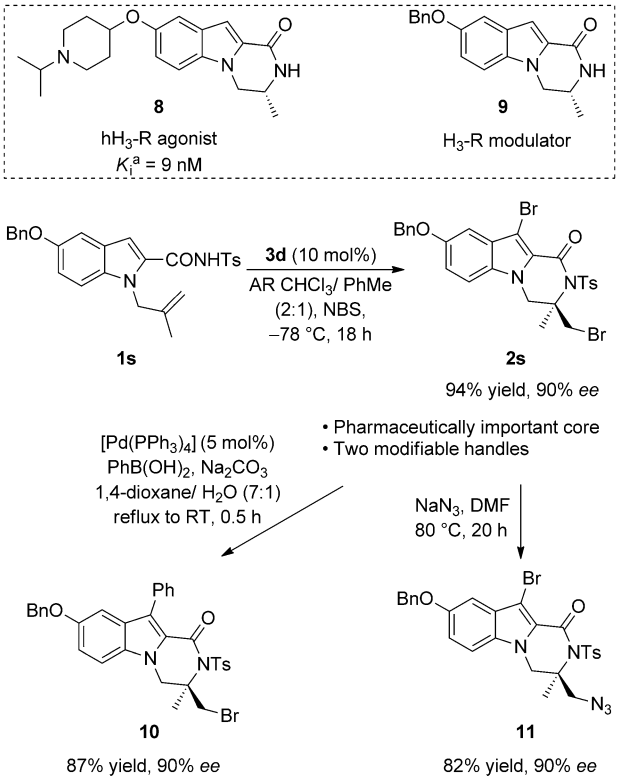


Figure 1. Molecular structure of compounds **2h** (left) and **5b** (right) in the solid state. Thermal ellipsoids are shown at 50% probability.



Scheme 1. Bromolactamization of the trisubstituted olefinic amide **6.**



Scheme 2. Direct synthesis of pharmaceutically important lactam core **2s** and subsequent transformations. DMF = *N*,*N*-dimethylformamide.

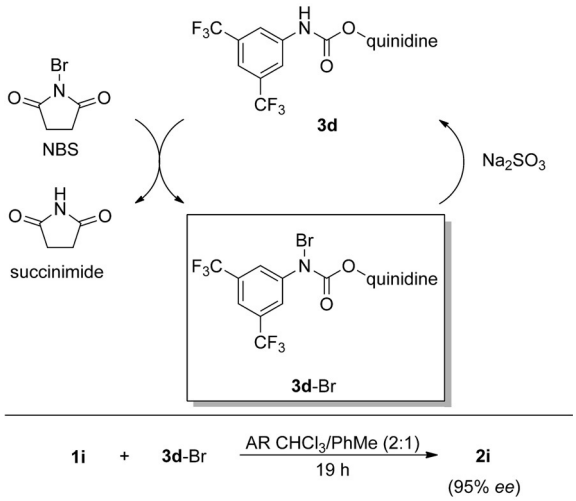
of **1s** gave **2s**, which has a tricyclic lactam core that commonly occurs in bioactive molecules, such as the highly potent histamine H_3 receptor agonist **8**[9b] and the H_3 receptor modulator **9**.[9f] **2s** contains two Br handles, each of which

could be selectively modified. For instance, palladium-catalyzed coupling reaction of **2s** could functionalize the C3 position of the indole moiety to give **10**. In contrast, substitution with azide on the methylene bromide of **2s** yielded **11**, in which the alkyl azide handle is a common click partner for bioimaging uses.[14] These reactions are thus valuable in the rapid synthesis of a large diversity of bioactive molecule analogues for the drug screening process.

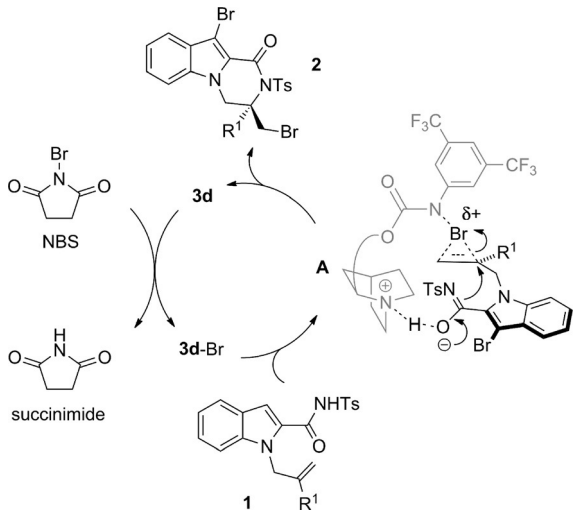
To obtain insight into the reaction mechanism, a ^{1}H NMR study was performed on a 1:1 mixture of **3d** and NBS. Close examination of the NMR spectrum revealed a distinctly new species.[11] When a sample of this mixture was subjected to high-resolution mass spectrometry (HRMS), the mass of the new species was found to be equal to that of brominated **3d**. In addition, when subjecting the new species in aqueous Na_2SO_3, **3d** could be regenerated quantitatively, thus suggesting that the Br in the new species is electrophilic in bromination reaction. As **3d** contains a relatively acidic N-H proton, we speculated that one possibility is that the N-H might exchange with NBS to form the N-Br species, that is, **3d**-Br (Scheme 3).[15,16]

To gain a better understanding on the reaction, **3d** was mixed with the stronger brominating agent 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) (1:1),[17] and the same mass value corresponding to the new species could also be detected by HRMS. In a further experiment, we subjected **1i** to a stoichiometric amount of **3d**-Br which was generated in situ from a 1:1 mixture of **3d** and TBCO (Scheme 3). After 19 h, **2i** was formed with the same *ee* value as that of the reaction performed using a catalytic amount of **3d** and stoichiometric halogen source NBS (Table 4, entry 10).[11]

Based on these observations, we suspected that **3d**-Br could be the active brominating species in the reaction. This process is different from the mechanistic proposals in our previous studies on thiocarbamates, where the Lewis-basic sulfur could interact with the Br on NBS during the process of the enantioselective bromocyclization reactions.[10] Although the establishment of a very detailed mechanistic picture demands further experimentation, we attempted to construct a preliminary proposal of the catalytic cycle by piecing our



Scheme 3. Bromine exchange between **3d** and NBS.



Scheme 4. A plausible reaction mechanism.

current data together. This mechanistic proposal is depicted in Scheme 4. At this stage, we believe that the first step might involve a halogen exchange between **3d** and NBS to give the chiral brominating species **3d**-Br. The amide in **1**, which contains an acidic proton, as a result of the electron-withdrawing Ts group, might then hydrogen bond to the quinuclidine nitrogen atom of **3d**-Br to give species **A**.[16] We speculated that the OH in the imidic acid (tautomer of amide) of the substrate **1** might be a better hydrogen-bond donor to the hard base quinuclidine,[6] thus allowing the softer imidic nitrogen base to attack the bromonium and yield the lactam product **2**. The role of ethanol, however, remains unclear and will be the subject of further investigations.[12]

In summary, we have developed an enantioselective bromolactamization using a carbamate as the catalyst, thus resulting in the formation of lactams with up to two stereogenic centers. The reaction rate and enantioselectivity was promoted by EtOH additive. The antipode of the lactam product could be obtained by a simple switch to the pseudoenantiomeric form of the catalyst. To the best of our knowledge, this represents the first case of organocatalytic enantioselective bromolactamization that proceeds with N-cyclization, thus leading to the formation of highly enantioenriched bromolactams.[18] This report also details the first effective use of a carbamate as an organocatalyst. Intensive studies on the mechanism of the carbamate catalysis are underway.

Acknowledgements

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[11] The details appear in the Supporting Information.

[12] The *ee* value of the bromolactamization product was highly dependent on the size of the alcohol additive, and much lower conversion was observed when a sterically bulky alcohol was used. In addition, the use of Et_2O in place of EtOH as the additive led to a significant reduction in *ee* value, thus suggesting that the hydroxy group of EtOH might play a crucial role in the reaction. Thus, we speculate that the ethanol might involve in the enantiodetermining step with the involvement of hydrogen bonding. For details, see the Supporting Information.

[13] CCDC 1063550 (**2h**) and 1063551 (**5b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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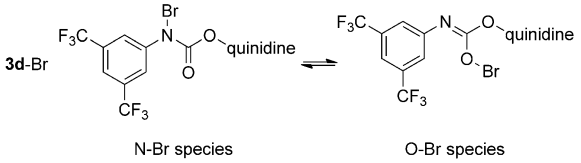
[16] Since carbamate can undergo tautomerization, we cannot rule out the possibility that **3d**-Br might exist as the form of O-Br species instead of N-Br species.



[17] Although the reaction rate between **3d** and NBS was slow, the reaction rate between **3d** and bromine source could be greatly enhanced by replacing NBS with TBCO.

[18] We also attempted to cyclize an olefinic amide with a benzene core instead of an indole. The corresponding bromolactam could be obtained in good yield and appreciable enantioselectivity. For details, see the Supporting Information.

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