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Enantioselective Chloro-*O*-cyclization of Unsaturated *N*-Tosylcarbamates

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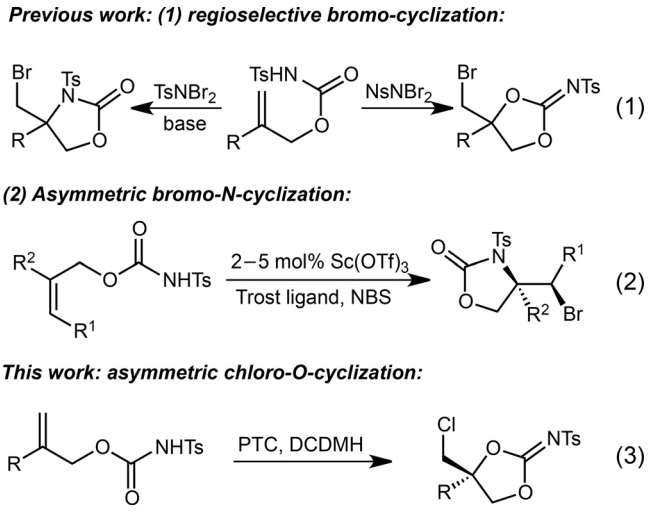
Abstract: An enantioselective chloro-*O*-cyclization of unsaturated *N*-tosylcarbamates has been developed for the first time using a *Cinchona*-derived quaternary ammonium salt as the catalyst, the desired enantioenriched chloromethyldioxolanimines were prepared with excellent regioselectivities and high enantioselectivities.

Keywords: asymmetric catalysis; cyclization; electrophilic addition; halogenation; regioselectivity

Electrophilic halogenations of alkenes are valuable synthetic transformations in organic synthesis for the preparation of halogenated compounds.[1] In recent years catalytic the enantioselective halofunctionalization of alkenes has received considerable attention. Many remarkable endeavours have been made to develop catalytic systems for asymmetric halogenation reactions.[2] Mechanism studies have demonstrated that the generation of an enantiomerically enriched halonium ion (Cl, Br, I) intermediate is crucial for the successful asymmetric halogenation of an alkene.[2,3] In general, catalytic strategies of halofunctionalization reactions by using chiral Lewis bases,[4] chiral Lewis acids[5] and chiral Brønsted acids[6] as catalysts have been developed, in which the halogen sources are activated in a chiral environment, and the organocatalytic approach is gaining prominence with promising results. On the other hand, phase-transfer catalysts (PTCs) have also been used in asymmetric halogenation reactions, wherein the halogen sources and substrates are brought together by the PTCs. In 2004, Gao and co-workers reported the first organocatalytic asymmetric halogenation of alkenes using *Cinchona*-derived quaternary ammonium salt as a phase-transfer catalyst.[7] Altough Toste and co-workers and others have developed asymmetric halogenation reactions by using anionic phase-transfer catalyst,[6e,f,8] traditional PT-catalyzed asymmetric halofunctionalizations of alkenes have received little attention.[9]

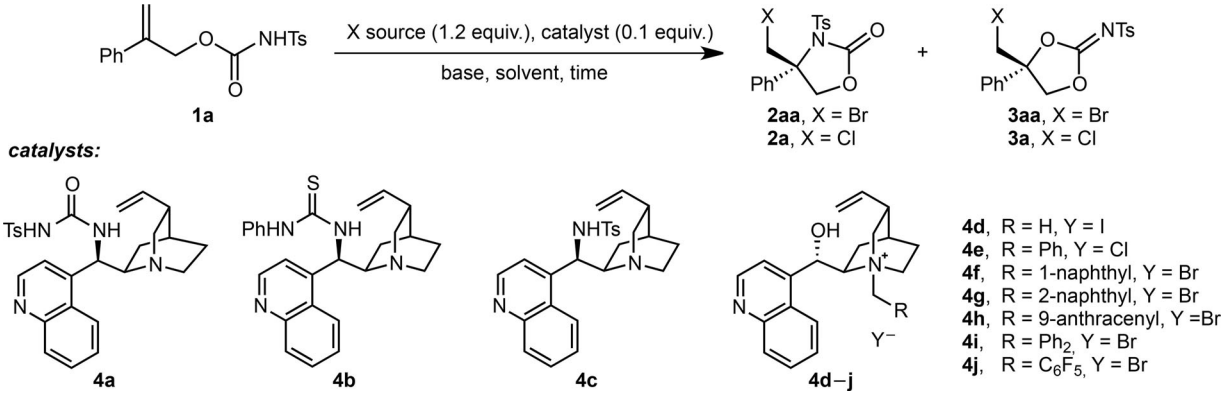
Halocyclization of unsaturated substrates having ambident nucleophilic groups such as amides or carbamates can give mixtures of *N*- and *O*-cyclization products. To date, halo-*O*-cyclization and halo-*N*-cyclization of unsaturated amides have been well documented.[10] Based on the hard/soft acid base theory, the *O*-cyclization takes place prior to the *N*-cyclization. However, halocyclization of unsaturated *N*-tosylcarbamates always returned a mixture of *N*- and *O*-cyclization products. Recently, we reported a regioselective bromocyclization of unsaturated *N*-tosylcarbamates promoted by *N,N*-dibromosulfonamides. Both *N*- and *O*-cyclization products were obtained with high yields and excellent regioselectivities [Scheme 1, Eq. (1)].[11] Shi and co-workers developed the bromo-*N*-cyclization of unsaturated *N*-tosylcarbamates by using a complex of $Sc(OTf)_3$ with Trost ligands



Scheme 1. Halocyclization of unsaturated *N*-tosylcarbamates.

[Scheme 1, Eq, (2)].[12] This protocol features exclusive *N*-cyclization, a broad substrate scope and high enantioselectivity.[12] In our efforts to further study the asymmetric cyclization of this substrate, we have found that chloro-*O*-cyclization products can be obtained with high enantioselectivities by using a *Cinchona*-derived quaternary ammonium salt as the catalyst [Scheme 1, Eq. (3)]. Herein we wish to report our preliminary results on the first enantioselective chloro-*O*-cyclization of unsaturated *N*-tosylcarbamates. Our initial studies were carried out with 2-phenylallyl tosylcarbamate (**1a**) as the test substrate (Table 1). On treatment of **1a** with *N*-bromosuccinimide (NBS) in the presence of 0.1 equiv. of urea **4a** in CH_2Cl_2 at room temperature for 12 h, both the bromo-*N*-cyclization product **2aa** and the bromo-*O*-

Table 1. Optimization of the enantioselective halocyclization of **1a**.[a]



Entry	Cat	X source	Base [equiv.]	Solvent	Time [h]	**2aa**, **2a** Yield [%][b]	*ee* [%]	**3aa**, **3a** Yield [%][b]	*ee* [%]
1	**4a**	NBS	–	CH_2Cl_2	12	44	5	38	11
2	**4a**	$TsNBr_2$	–	CH_2Cl_2	70	8	10	72	8
3	**4b**	$TsNBr_2$	–	CH_2Cl_2	70	24	0	53	6
4	**4c**	$TsNBr_2$	–	CH_2Cl_2	12	25	9	33	3
5	**4d**	$TsNBr_2$	–	CH_2Cl_2	12	23	4	58	2
6	**4e**	$TsNBr_2$	–	toluene	2	–[c]		69	40
7	**4e**	DBDMH	–	toluene	2	–		66	47
8	**4f**	DBDMH	–	toluene	2	–		95	18
9	**4g**	DBDMH	–	toluene	2	-		92	27
10	**4h**	DBDMH	–	toluene	2	–		65	0
11	**4i**	DBDMH	–	toluene	2	-		73	0
12	**4j**	DBDMH	–	toluene	12	–		96	21
13	**4e**	DCDMH	–	toluene	12	–		72	58
14	**4e**	NCS	–	toluene	12	trace		trace	
15	**4e**	DCDPH	–	toluene	12	–		51	58
16	**4e**	DCDMH	–	CH_2Cl_2	12	–		68	5
17	**4e**	DCDMH	–	THF	12	–		38	50
18	**4e**	DCDMH	–	benzene	12	–		75	56
19	**4e**	DCDMH	–	xylene	12	–		10	55
20	**4e**	DCDMH	–	chlorobenzene	12	–		82	53
21	**4e**	DCDMH	$K_3PO_4 \cdot 3H_2O$ (0.2)	toluene	12	–		79	72
22	**4e**	DCDMH	$K_3PO_4 \cdot 3H_2O$ (0.5)	toluene	12	–		80	71
23	**4e**	DCDMH	$K_2HPO_4 \cdot 3H_2O$ (0.5)	toluene	12	–		52	59
24	**4e**	DCDMH	K_2CO_3 (0.5)	toluene	12	–		65	27
25	**4e**	DCDMH	Na_3PO_4 (0.2)	toluene	12	–		71	71
26	**4e**	DCDMH	KPF_6 (0.2)	toluene	12	–		40	52
27[d]	**4e**	DCDMH	$K_3PO_4 \cdot 3H_2O$ (0.2)	toluene	65	–		89	89
28[d]	**4e**	DCDMH	$K_3PO_4 \cdot 3H_2O$ (0.2)	toluene/PhH 2:3	120	–		88	91

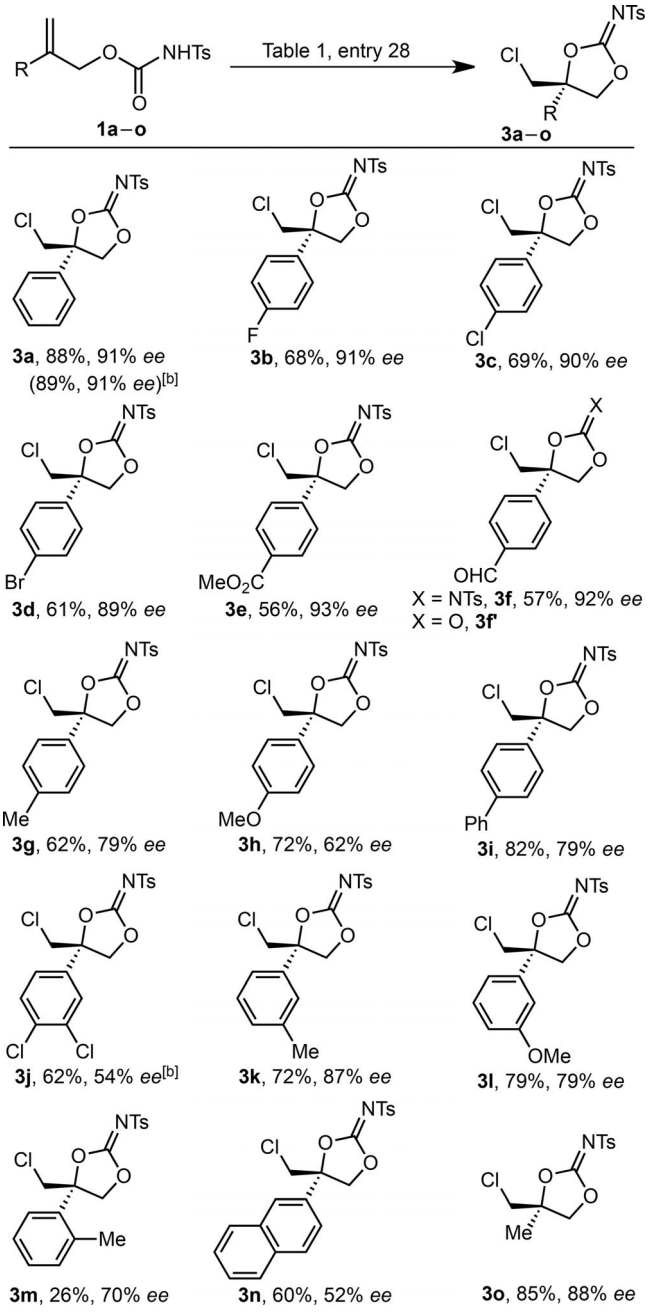
[a] Reactions were carried out with **1a** (0.20 mmol), catalyst (0.02 mmol) and X source (0.24 mmol) in solvent (10.0 mL) at room temperature in the absence of light.
[b] Isolated yield.
[c] The desired product was not isolated.
[d] The reaction temperature is −25 °C.

cyclization product **3aa** were obtained in 44% and 38% yields with 5% and 11% *ee*, respectively (entry 1). Encouraged by our recent studies on the regioselective bromocyclization of **1a** and related works by using *N,N*-dibromosulfonamides as reagents,[13] $TsNBr_2$ was employed as the halogen source. Indeed, the regioselectivity was improved significantly and **3aa** was obtained as the major cyclization product albeit with low *ee* (entry 2). Other organocatalysts **4b–d** all resulted in poor regioselectivities and enantioselectivities (entries 3–5). To our delight, **3aa** was obtained as the sole product with 40% *ee* when PTC **4e** was used in toluene (entry 6). On using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the bromine source, a measurable increase in *ee* was observed with the regioselectivity being maintained (entry 7). A series of *Cinchona*-derived PTCs was examined by using DBDMH as the bromine source. However, no positive results were obtained (entries 8–12). Surprisingly, PTCs bearing bulky substituents such as 9-anthracenyl and diphenylmethyl resulted in even no *ee* (entries 10 and 11).

After identification of the appropriate catalyst (**4e**), further investigation of other halogen reagents indicated that 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) was the most suitable halogen source for this cyclization reaction, and the desired chloro-*O*-cyclization product **3a** was obtained exclusively in 72% yield with 58% *ee* (entry 13). Only trace amounts of the cyclization products were observed when NCS was utilized as the halogen source (entry 14). 1,3-Dichloro-5,5-diphenylhydantoin (DCDPH) also returned 58% *ee* under the same reaction conditions, but with a measurable decrease in yield (entry 15 *vs.* 13). Among the solvents examined, toluene gave the best results (entries 13, 16–20). A series of additives were subsequently investigated (entries 21–26). Interestingly, a significant increase in enantioselectivity was detected when 0.2 equiv. of $K_3PO_4{\cdot}3H_2O$ was used as the additive (entry 21). A comparable *ee* was obtained when the additive loading was increased to 0.5 equiv. (entry 22). A similar result was obtained when 0.2 equiv. of $Na_3PO_4{\cdot}3H_2O$ was used as the additive (entry 25), indicating that the phosphate ion may play an important role in the enantioselectivity of this reaction (e.g., counter ion effect).[14] The *ee* was increased to 89% when the reaction was conducted at −25 °C (entry 27). Further optimization of this reaction by using different mixed solvents allowed us to discover the following optimal conditions: an 88% yield and 91% *ee* of **3a** was obtained when the reaction was conducted in toluene/benzene (2:3, 0.02 M) at −25 °C (entry 28).

With the optimized reaction conditions in hand, the substrate scope of this chloro-*O*-cyclization reaction was explored. As shown in Table 2, a broad range of aryl-substituted allyl tosylcarbamates could be converted to the corresponding chloro-*O*-cyclization products with good yields and moderate to high *ee*s. Substrates with electron-deficient substituents at the *para* positions of the phenyl ring offered excellent *ee*s (Table 2, **3a–f**) in which ester and aldehyde functional groups are both well tolerated. Notably, **3f** was hydrolyzed to **3f′** completely during NMR analysis.[15] Similar to previous observations on asymmetric halocycli-

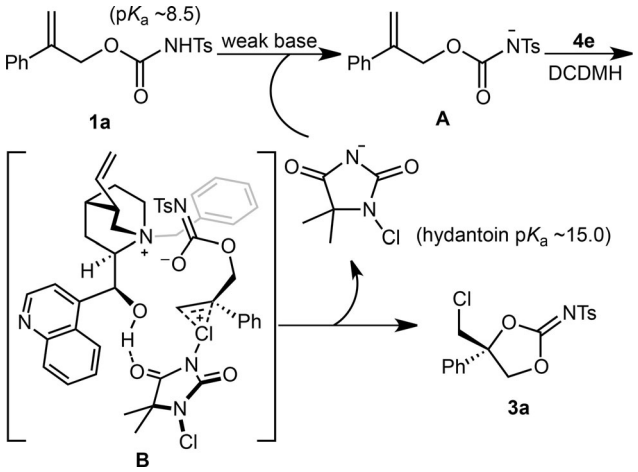
Table 2. Substrate scope for the enantioselective chloro-*O*-cyclization of **1**.[a]



[a] For the standard reaction conditions, see Table 1, entry 28, the yields are isolated yields.
[b] On a 2.0 mmol scale.

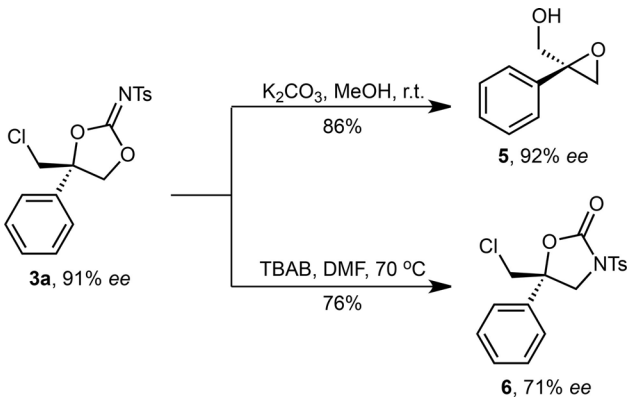
zation reactions,[2] electron-donating substituents at the *para* or *meta* positions resulted in decreased *ee*s (**3g–i**, **3k**, **3l**). However, the electron-deficient 3,4-dichlorinated substrate returned a moderate *ee* (**3j**). The existence of a substituent on the *ortho* position dramatically hampered the reaction (**3m**, **3n**), presumably because of steric hindrance. Satisfactorily, the alkyl-substituted substrate 2-methylallyl tosylcarbamate resulted in the desired product **3o** in 85% yield with 88% *ee*. Additionally, the reaction was readily scalable without losing any efficiency and enantioselectivity (**3a**).

While a precise understanding of the origin of the enantioselectivity needs further studies, a plausible transition state model is proposed in Scheme 2. The deprotonation of tosylcarbamate **1a** by a weak base forms intermediate **A**.[16] Then **A** could interact with **4e** and DCDMH to give transition state **B**, where a chiral environment is probably created by an ion pair and a hydrogen bond between the hydroxy group and DCDMH. Notably, the hydroxy group in the catalyst plays an important role in the enantioselectivity. When the hydroxy group in **4e** was benzylated, the model reaction shown in Table 1 gave **3a** in 65% yield with only 5% *ee*. Finally, nucleophilic attack of the carbamate anion on the chloronium ion yields the product **3a**.



Scheme 2. Proposed mechanism.

To demonstrate the synthetic utility and determine the absolute configuration of **3**, dioxolanimine **3a** was transformed to epoxide **5** smoothly. The absolute configuration of **3a** was determined by comparing the optical rotation of **5** and HPLC trace with the reported ones.[17] Furthermore, rearrangement of **3a** with TBAB gave **6** in good yield albeit with some racemization (Scheme 3). The *ee* erosion may be due to halogen exchange during the reaction, this assumption is supported by a control experiment, where the reaction of **3a** with LiCl (1.2 equiv.) in DMF gave the racemic product **6** in 78% yield.



Scheme 3. Transformation of **3a** to compounds **5** and **6**.

In summary, we have developed an efficient catalytic enantioselective chloro-*O*-cyclization of unsaturated *N*-tosylcarbamates using a *Cinchona*-derived PTC catalyst for the first time. A series of enantioenriched 4-chloromethyl-1,3-dioxolan-2-imines were prepared with good yields and good to high enantioselectivities. Further investigations to better understand the mechanism, and to extend the scope and application of this chlorocyclization reaction are underway.

Experimental Section

General Procedure for the Chloro-*O*-cyclization of Unsaturated *N*-Tosylcarbamates to 4-Aryl-4-chloromethyl-1,3-dioxolan-2-tosylimines 3 (Table 2)

To a solution of allylic unsaturated *N*-tosylcarbamate **1** (0.20 mmol, 1.00 equiv.), catalyst **4e** (8.4 mg, 0.02 mmol, 0.10 equiv.) in toluene/benzene (2:3, 10.0 mL) at −25 °C in the dark under N_2 was added 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) (47.3 mg, 0.24 mmol, 1.20 equiv.). The resulting mixture was stirred at −25 °C for 120 h. The reaction was quenched with saturated Na_2SO_3 (3.0 mL) at −25 °C and then was warmed to 25 °C. The solution was diluted with water (3.0 mL) and extracted with EtOAc (3 × 6 mL). The combined extracts were washed with brine (10.0 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether, EtOAc) to yield the corresponding product **3**.

Acknowledgements

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