Communication

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Enantioselective Bromoaminocyclization of Allyl *N*-Tosylcarbamates Catalyzed by Chiral Phosphine-Sc(OTf)$_3$ Complex

Deshun Huang,[a] Xiaoqin Liu,[a] Lijun Li,[a] Yudong Cai,[a] Weigang Liu,[a] and Yian Shi*[a,b]

[a] Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China. [b] Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States

Supporting Information Placeholder

ABSTRACT: An effective enantioselective bromoaminocyclization of allyl *N*-tosylcarbamates catalyzed by chiral phosphine-Sc(OTf)$_3$ is described. A wide variety of optically active oxazolidinone derivertives containing various functional groups can be obtained in high enantioselectivities.

Electrophilic halogenation of olefins is one of the most fundamental reactions in organic chemistry and provides a very effective approach to functionalize the C–C double bonds.[1] Asymmetric halogenation allows the installation of two chiral C–X bonds simultaneously. The resulting halides can undergo a variety of transformations, particularly stereoselective nucleophilic substitutions, which make them extremely versatile chiral building blocks in organic synthesis. In addition, halogens are contained in many important natural[2] and unnatural products. Due to its importance, asymmetric halogenation of olefins has received considerable attention. Recently, significant progress has been made in this area.[3] A number of catalytic systems including chiral Lewis acid,[4,5] amine,[6-11] phosphoric acid,[12-14] and Pd(II) complex[15] via various asymmetric induction mechanisms, have been developed. However, there are still many unsolved challenges. Development of new catalytic systems with new types of substrates is highly desirable. During our own efforts on catalytic electrophilic additions to olefins (Scheme 1),[13a,16] we have found that chiral phosphine-Sc(OTf)$_3$ is an effective catalyst for asymmetric bromoaminocyclization of allyl *N*-tosylcarbamates. Herein, we wish to report our preliminary studies on this subject.

Scheme 1. Catalytic electrophilic additions to olefins

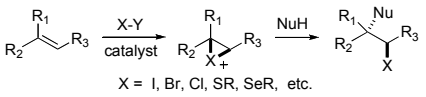
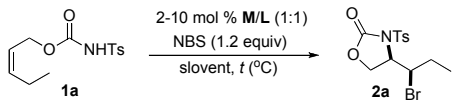


Table 1. Studies on reaction conditions[a]



entry	L	M	solvent	t (°C)	yield%[b]	ee%[c]
1	**L1**	$Cu(OTf)_2$	PhMe	0	14	-7
2	**L1**	$Sm(OTf)_3$	PhMe	0	72	-6
3	**L1**	$Y(OTf)_3$	PhMe	0	68	12
4	**L1**	$Sc(OTf)_3$	PhMe	0	55	4
5[d]	**L2**	$Sc(OTf)_3$	PhMe	-30	25	4
6	**L3**	$Sc(OTf)_3$	PhMe	-30	31	-9
7	**L4**	$Sc(OTf)_3$	PhMe	-30	70	-31
8	**L5**	$Sc(OTf)_3$	PhMe	-30	61	93
9	**L5**	$Y(OTf)_3$	PhMe	-30	54	-23
10	**L5**	$Cu(OTf)_2$	PhMe	-30	7	3
11	-	-	PhMe	-30	trace	/
12	-	$Sc(OTf)_3$	PhMe	-30	trace	/
13	**L5**	-	PhMe	-30	54	-2
14	**L5**	$Sc(OTf)_3$	DCM	-30	58	82
15	**L5**	$Sc(OTf)_3$	$CHCl_3$	-30	70	88
16	**L5**	$Sc(OTf)_3$	THF	-30	10	80
17[e]	**L5**	$Sc(OTf)_3$	PhMe	-40	60	94
18[f]	**L5**	$Sc(OTf)_3$	PhMe	-50	45	96
19[g]	**L5**	$Sc(OTf)_3$	PhMe/DCM (3:1)	-50	63	96
20[h]	**L5**	**$Sc(OTf)_3$**	**PhMe/DCM (3:1)**	**-50**	**87**	**96**
21[h]	**L6**	$Sc(OTf)_3$	PhMe/DCM (3:1)	-50	84	97

[a] The reactions were carried out with **1a** (0.10 mmol), NBS (0.12 mmol), and **M**/**L** (1:1, 0.010 mmol) in solvent (1.0 mL) for 18 h unless otherwise stated. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] With **L2** (0.020 mmol). [e] For 36 h. [f] For 72 h. [g] For 48 h. [h] With $Sc(OTf)_3$/**L** (1:1, 0.0020 mmol) for 48 h.

Our initial studies were carried out with *cis*-pent-2-en-1-yl tosylcarbamate (**1a**) as substrate and NBS as bromine source (Table 1). A variety of commonly used

chiral Lewis acids were first examined.[17] Only modest ee's were generally obtained, with M-PyBox (**L1**)[18a] (Figure 1) being among the best (Entries 1-4). Subsequently, Lewis acids with chiral phosphine ligands were investigated (Entries 5-10).[18b-f] To our delight, oxazolidinone **2a** was obtained in 61% yield and 93% ee with 10 mol% $Sc(OTf)_3$ and Trost ligand **L5** in PhMe at -30 °C (Entry 8). Control experiments showed that little conversion was observed without $Sc(OTf)_3$ and **L5** (Entry 11) or with $Sc(OTf)_3$ alone (Entry 12). However, ligand **L5** itself was able to catalyze the reaction, giving nearly racemic **2a** (Entry 13).[19] The reaction was further optimized with solvent and temperature (Entries 14-19). Oxazolidinone **2a** was obtained in 63% yield and 96% ee with 10 mol% $Sc(OTf)_3$-**L5** in PhMe/DCM (3:1) at -50 °C (Entry 19). Decreasing the catalyst loading to 2 mol% led to a cleaner reaction, thus increasing the yield to 87% without loss of ee (Entry 20).[20] Similar result was also obtained with Trost ligand **L6** (Entry 21). Other halogen sources were also examined (Scheme 2).[21] Comparable yields and ee's were obtained with DBDMH and NBP. However, no reactions were observed with TBCO, NCS, or NIS.

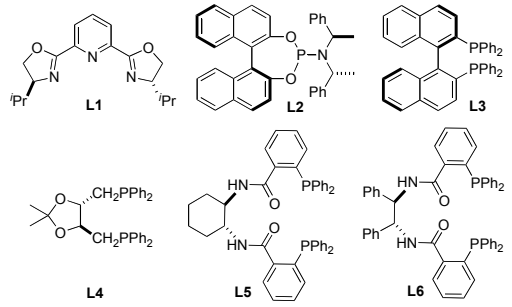
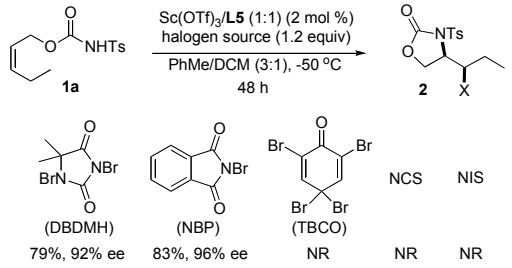


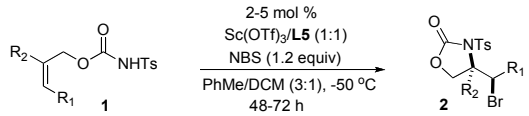
Figure 1. Selected examples of chiral ligands examined

Scheme 2. Effect of halogen source



As shown in Table 2, the enantioselective bromoaminocyclization can be extended to a wide variety of *cis*-allyl *N*-tosylcarbamates to form the corresponding oxazolidinones in 50-90% yields and 92-97% ee's with 2-5 mol% $Sc(OTf)_3$-**L5** (Entries 1-14). The substituents on the olefin can be linear alkyl groups (Entries 1-4) as well as branched alkyl groups (Entries 5&6). Various functional groups, such as OBn, OAc, OTs, CN, Cl, and NHBoc, can be present in the side chains (Entries 7-12). Alkyne and α,β-unsaturated ester can also be tolerated (Entries 13&14). Terminal allyl *N*-tosylcarbamate **1o** was also effective substrate to give oxazolidinone **2o**

Table 2. Enantioselective bromoaminocyclization of allyl *N*-tosylcarbamates[a]



entry	substrate	product[b]	yield%[c]	ee%[d]
1	R_1 = Et, **1a**	**2a**	88	96
2	R_1 = *n*-Bu, **1b**	**2b**	80	96
3	R_1 = *n*-C_6H_{13}, **1c**	**2c**	90	96
4	R_1 = CH_2Bn, **1d**	**2d**	83	93
5	R_1 = CH_2Cp, **1e**	**2e**	77	96
6	R_1 = Cy, **1f**	**2f**	71	96
7	R_1 = CH_2OBn, **1g**	**2g**	80	94
8	X = OAc, **1h**	**2h**	80	97
9	X = OTs, **1i**	**2i**	75	97
10	X = CN, **1j**	**2j**	75	96
11	X = Cl, **1k**	**2k**	87	96
12	X = NHBoc, **1l**	**2l**	50	92
13	**1m**	**2m**	81	94
14	**1n**	**2n**	86	95
15	**1o**	**2o**	87	89
16	R_1 = Me, **1p**	**2p**	81	83
17	R_1 = *n*-Bu, **1q**	**2q**	83	91
18	R_1 = *i*-Bu, **1r**	**2r**	87	88
19	**1s**	**2s**	48 (**2s**)	5 (**2s**)
		2t	20 (**2t**)	90 (**2t**)

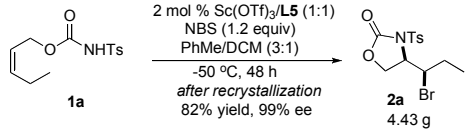
[a] The reactions were carried out with **1** (0.50 mmol), NBS (0.60 mmol), and $Sc(OTf)_3$/**L5** (1:1, 0.010 mmol) in PhMe/DCM (3:1) (5.0 mL) at -50 °C for 48 h unless otherwise stated. For entries 14, 17, and 18, the reactions were carried out for 72 h. For entries 15 and 19, the reactions were carried our with $Sc(OTf)_3$/**L5** (1:1, 0.025 mmol) for 48 h. For entries 6, 7, and 13, the reactions were carried out with $Sc(OTf)_3$/**L5** (1:1, 0.025 mmol) for 72 h. [b] The absolute configurations of **2a**, **2r**, and **2t** were determined by the X-ray structures. The absolute configurations of **2g** and **2o** were determined by comparing the optical rotations with literature after being converted to the corresponding aziridines. The abso-

lute configurations of the others except **2s** were tentatively proposed by analogy. The stereochemistry of **2s** indicated represents the relative stereochemistry. [c] Isolated yield. [d] Determined by chiral HPLC analysis.

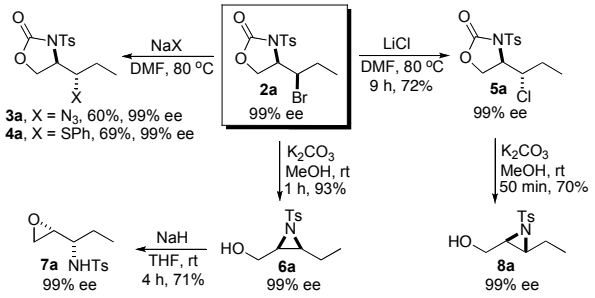
in 87% yield and 89% ee (Entry 15). The reaction can also be applied to (*Z*)-trisubstituted olefins, giving the products in 81-87% yields and 83-91% ee's (Entries 16-18). In all the cases, the reactions proceeded regioselectively to give the 5-*exo* products. However, a mixture of 5-*exo* and 6-*endo* products with different ee's were obtained with the *trans* substrate examined (Entry 19).

The reaction can be carried out on a relatively large scale. For example, 4.43 g oxazolidinone **2a** was obtained in 82% yield and 99% ee after recrystallization (Scheme 3). The resulting bromide can be displaced by nucleophiles, such as azide, benzenethiolate, and chloride with inversion of configuration (Scheme 4). Treating bromide **2a** with K_2CO_3 in MeOH led to *cis*-aziridine **6a**,[22] which can undergo aza-Payne rearrangement[23] to form epoxide **7a**. Both **6a** and **7a** are highly useful intermediates.[23,24] Like bromide **2a**, chloride **5a** can be converted to the corresponding *trans*-aziridine **8a**. To certain extent, the availability of chloride **5a** provides an alternative solution to *trans* substrates, which are not effective with the current catalytic system. As exemplified by aziridine **6f** in Scheme 5, the Ts group can be readily removed without loss of ee with Mg in MeOH under sonication.

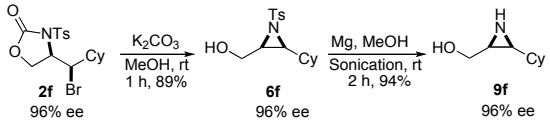
Scheme 3. Bromoaminocyclization on gram scale



Scheme 4. Synthetic transformations of bromide 2a

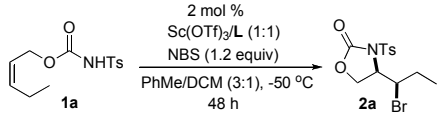


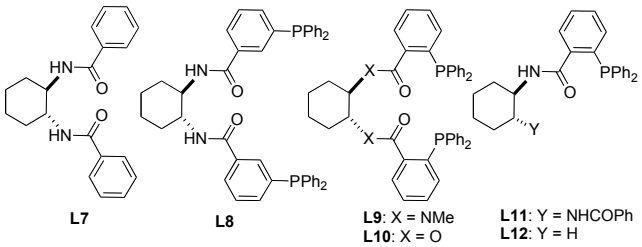
Scheme 5. Removal of Ts group



To gain some mechanistic insights into this catalytic system, several analogues (**L7**-**L12**) of ligand **L5** were prepared and examined for the reaction with substrate **1a** (Table 3). Little or low yield and ee were obtained with **L7** and **L8** (Table 3, entries 1&2), illustrating that the phoshine group and its position are crucial for the reaction. The dramatically reduced yields and ee's obtained with **L9** and **L10** (Table 3, entries 3&4) as compared to **L5** (Table 2, entry 1) indicate that the secondary amide is very important for the reactivity and enantioselectivity. As shown by the results of **L11** and **L12** (Table 3, entries 5&6), the bisphosphine and bisamide moieties are essential to the reaction efficiency. The catalytic properties of **L7**-**L12** in the absence of $Sc(OTf)_3$ were also investigated (Table 3, entries 7-12). In contrast to **L8**-**L12**, no reaction was observed for **L7**, which suggests that the phosphine is possibly involved in the activation of NBS. There are some interactions between the phosphine and Sc or NBS as detected by ^{31}P NMR spectra of ligand **L5** with $Sc(OTf)_3$ and/or NBS (Supporting Information). It appears that $Sc(OTf)_3$ could coordinate with both **L5** and the substrate to allow the bromoaminocyclization to occur in a chiral environment via activation of NBS by the phosphine and/or Sc. A precise understanding of the reaction mode and the origin of the enantioselectivity for the current system await further study.

Table 3. The structural effect of ligand[a]





entry	ML	yield%[b]	ee%[c]	entry	L	yield%[b]	ee%[c]
1[a]	**L7**	NR	/	7[d]	**L7**	NR	/
2[a]	**L8**	8	-6	8[d]	**L8**	12	-8
3[a]	**L9**	14	40	9[d]	**L9**	39	4
4[a]	**L10**	7	2	10[d]	**L10**	43	5
5[a]	**L11**	47	9	11[d]	**L11**	45	0
6[a]	**L12**	trace	/	12[d]	**L12**	57	/

[a] The reactions were carried out with **1a** (0.50 mmol), NBS (0.60 mmol), and $Sc(OTf)_3$/**L** (1:1, 0.010 mmol) in PhMe/DCM (3:1) (5.0 mL) at -50 °C for 48 h unless otherwise stated. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Without $Sc(OTf)_3$.

In summary, we have developed an efficient enantioselective bromoaminocyclization of allyl *N*-tosylcarbamates using NBS as bromine source and $Sc(OTf)_3$-**L5** complex as catalyst. A wide variety of oxazolidinones with various functional groups can be obtained in generally good yields and high enantioselectivities. The reaction can be performed on a gram scale. Further transformations of these compounds provide access to useful intermediates with diverse functionality. Future efforts will be devoted to understanding the reaction mechanism, expanding the substrate scope, and exploring additional electrophilic addition processes.

ASSOCIATED CONTENT

Supporting Information.
Experimental procedures, characterization data, X-ray structures, data for determination of enantiomeric excess, and NMR spectra. This information is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

yian@lamar.colostate.edu

No competing financial interests have been declared.

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(19) Ligands **L1**-**L4** and **L6** can also catalyze this reaction but with low ee's (Table S1 in Supporting Information).

(20) No decomposition was observed when oxazolidinone **2a** was subjected to the reaction conditions.

(21) The reactions were carried out with **1a** (0.50 mmol), halogen source (0.60 mmol), and $Sc(OTf)_3$/**L5** (1:1, 0.010 mmol) in PhMe/DCM (3:1) (5.0 mL) at -50 ^{o}C for 48 h.

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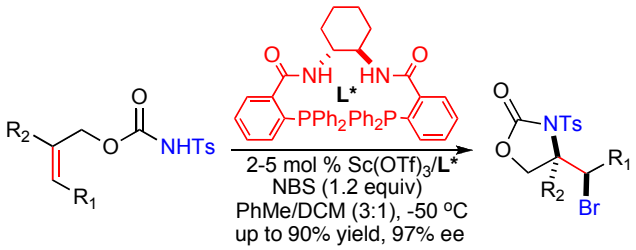
R2
R1
O
NHTs
NH
HN
L*
PPh2Ph2P
2-5 mol % Sc(OTf)3/L*
NBS (1.2 equiv)
PhMe/DCM (3:1), -50 °C
up to 90% yield, 97% ee
NTs
R1
R2
Br