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

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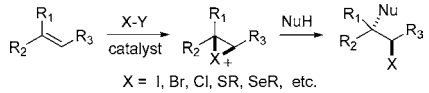
Supporting Information

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

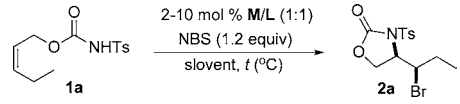
Electrophilic halogenation of olefins is one of the most fundamental reactions in organic chemistry and provides a very effective approach for functionalization of C–C double bonds.[1] Asymmetric halogenation allows the installation of two chiral C–X bonds simultaneously. The resulting halides can undergo 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. Because of 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] catalysts with various asymmetric induction mechanisms, have been developed. However, there are still many unsolved challenges. The development of new catalytic systems with new types of substrates is highly desirable. During our investigations of catalytic electrophilic additions to olefins (Scheme 1),[13a,16] we have found that a chiral phosphine–$Sc(OTf)_3$ complex is an effective catalyst for asymmetric bromoaminocyclization of allyl *N*-tosylcarbamates. Herein we report our preliminary studies on this subject.

Scheme 1. Catalytic Electrophilic Additions to Olefins



Our initial studies were carried out with *cis*-pent-2-en-1-yl tosylcarbamate (**1a**) as the substrate and *N*-bromosuccinimide (NBS) as the 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 with 93% ee using 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

Table 1. Studies of the Reaction Conditions[a]



1a 2a

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 yields. [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.

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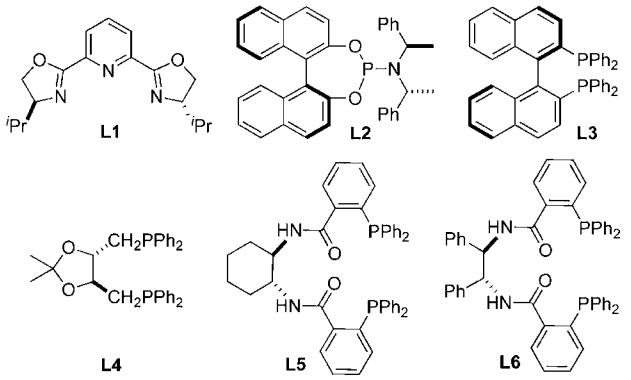
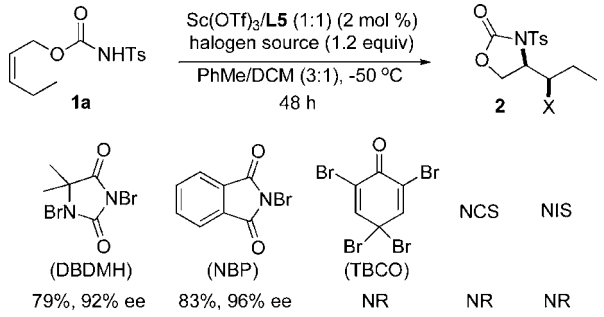


Figure 1. Selected examples of chiral ligands examined.

respect to solvent and temperature (entries 14–19). Oxazolidinone **2a** was obtained in 63% yield with 96% ee using 10 mol % $Sc(OTf)_3$–**L5** in 3:1 PhMe/dichloromethane (DCM) 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 results were obtained with Trost ligand **L6** (entry 21). Other halogen sources were also examined (Scheme 2).[21] Comparable yields

Scheme 2. Effect of the Halogen Source

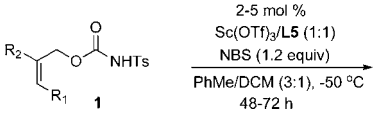


and ee's were obtained with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and *N*-bromophthalimide (NBP). However, no reactions were observed with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO), *N*-chlorosuccinimide (NCS), or *N*-iodosuccinimide (NIS).

As shown in Table 2, the enantioselective bromoaminocyclization could be extended to a wide variety of *cis*-allyl *N*-tosylcarbamates to form the corresponding oxazolidinones in 50–90% yield with 92–97% ee using 2–5 mol % $Sc(OTf)_3$–**L5** (entries 1–14). The substituents on the olefin can be linear (entries 1–4) or branched (entries 5 and 6) alkyl groups. 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 groups were also tolerated (entries 13 and 14). Terminal allyl *N*-tosylcarbamate **1o** was also an effective substrate, giving oxazolidinone **2o** in 87% yield with 89% ee (entry 15). The reaction could also be applied to *Z*-trisubstituted olefins, which gave the products in 81–87% yield with 83–91% ee (entries 16–18). In all 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 was obtained with the trans substrate examined (entry 19).

The reaction can be carried out on a relatively large scale. For example, 4.43 g of oxazolidinone **2a** was obtained in 82% yield with 99% ee after recrystallization (Scheme 3). The resulting

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 3:1 PhMe/DCM (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 out 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 from their X-ray structures. The absolute configurations of **2g** and **2o** were determined by comparing the optical rotations with literature values after they were converted to the corresponding aziridines. The absolute configurations of the others except **2s** were tentatively proposed by analogy. The indicated stereochemistry of **2s** represents the relative stereochemistry. [c]Isolated yields. [d]Determined by chiral HPLC analysis.

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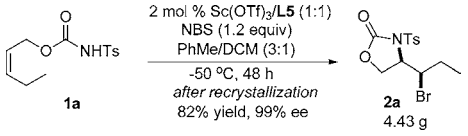
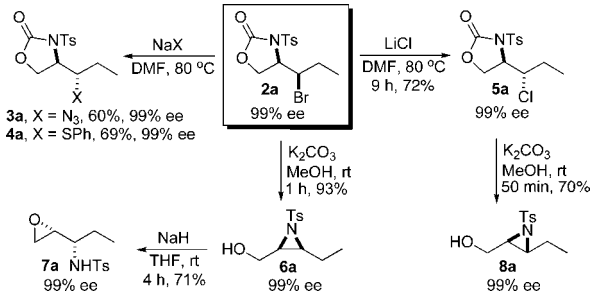
Scheme 3. Bromoaminocyclization on a Gram Scale



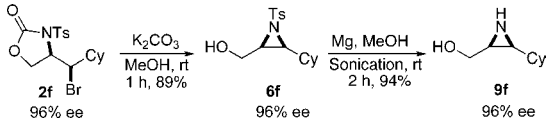
bromide can be displaced by nucleophiles such as azide, benzenethiolate, and chloride with inversion of configuration (Scheme 4). Treating bromide **2a** with K_2CO_3 in MeOH led to

Scheme 4. Synthetic Transformations of Bromide 2a



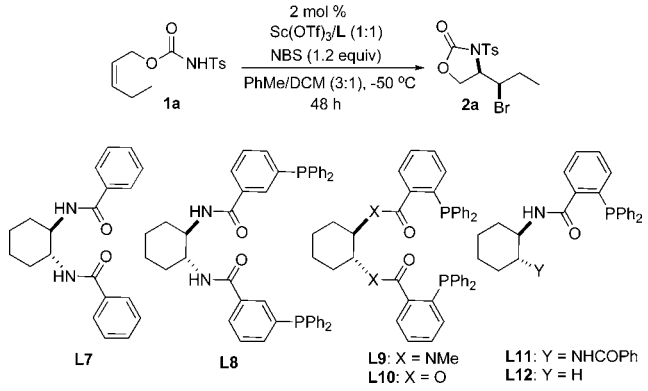
cis-aziridine **6a**,[22] which can undergo aza-Payne rearrangement[23] to form epoxide **7a**. Both **6a** and **7a** are highly useful intermediates.[23,24] Like bromide **2a**, chloride **5a** can be converted to the corresponding *trans*-aziridine **8a**. To a certain extent, the availability of 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 using Mg in MeOH under sonication.

Scheme 5. Removal of the Ts Group



To gain some mechanistic insights into this catalytic system, several analogues of ligand **L5** (**L7**–**L12**) were prepared and examined for the reaction with substrate **1a** (Table 3). Little or no yield and ee were obtained with **L7** and **L8** (Table 3, entries 1 and 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 and 4) relative to **L5** (Table 2, entry 1) indicate that the secondary amide is very important for the reactivity and enantioselectivity. As shown by the results obtained using **L11** and **L12** (Table 3, entries 5 and 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 with **L7**, which suggests that the phosphine may be involved in the activation of NBS. Some interactions between the phosphine and Sc or NBS were detected by ^{31}P NMR spectroscopy of ligand **L5** in the presence of $Sc(OTf)_3$ and/or NBS (see the Supporting Information). It appears that $Sc(OTf)_3$ can coordinate with both **L5** and the substrate to

Table 3. Structural Effect of the Ligand[a]



entry	L	yield (%)[b]	ee (%)[c]	entry	L	yield (%)[b]	ee (%)[c]
1	**L7**	NR	–	7[d]	**L7**	NR	–
2	**L8**	8	−6	8[d]	**L8**	12	−8
3	**L9**	14	40	9[d]	**L9**	39	4
4	**L10**	7	2	10[d]	**L10**	43	5
5	**L11**	47	9	11[d]	**L11**	45	0
6	**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 3:1 PhMe/DCM (5.0 mL) at −50 °C for 48 h, unless otherwise stated. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]Without $Sc(OTf)_3$.

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 in the current system awaits further study.

In summary, we have developed an efficient enantioselective bromoaminocyclization of allyl *N*-tosylcarbamates using NBS as the bromine source and the $Sc(OTf)_3$–**L5** complex as the catalyst. A wide variety of oxazolidinones with various functional groups were obtained in generally good yields with 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 the determination of enantiomeric excess, NMR spectra, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(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 3:1 PhMe/DCM (5.0 mL) at −50 °C for 48 h.

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