

Enantioselective 6-*exo*-Bromoaminocyclization of Homoallylic *N*-Tosylcarbamates Catalyzed by a Novel Monophosphine-Sc(OTf)₃ Complex

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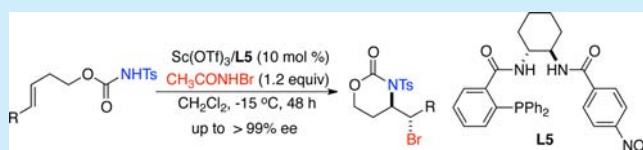
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Supporting Information

ABSTRACT: A highly enantioselective 6-*exo*-bromoamino-cyclization of (*E*)-homoallylic *N*-tosylcarbamates catalyzed by a novel monophosphine-Sc(OTf)₃ complex is described, giving a wide variety of optically active oxazinanones with high enantioselectivities.



Electrophilic halofunctionalization of olefins, one of the most fundamental organic reactions, allows the direct installation of two functional groups onto C–C double bonds in a stereoselective manner.¹ The resulting halides provide versatile intermediates for further transformations in organic synthesis. In recent years, asymmetric halogenation of olefins has received extensive attention,² which results in the development of various effective catalytic systems, including chiral Lewis acid,^{3,4} chiral phosphoric acid or phosphate,^{5,6} and chiral base.^{7,8} Despite that significant progress has been made in this area, developing new catalytic systems to address unsolved challenges is highly desirable. During our studies, we have discovered that a Sc(OTf)₃-L1 (Trost ligand⁹) complex is an effective catalyst for asymmetric bromocyclization of (*Z*)-allyl *N*-tosylcarbamates (**1**) (Scheme 1) (Figure 1).^{10a}

Mechanistic studies showed that the catalyst has stringent structural requirements for the ligand for the aforementioned bromocyclization. Two phosphines are essential for the reaction. To our surprise, optically active 1,3-oxazinan-2-ones (**4**) could be obtained with a monophosphine-Sc(OTf)₃ complex, but not with a Sc(OTf)₃-L1 complex when (*E*)-homoallylic *N*-tosylcarbamates (**3**) were used as the substrate (Scheme 2). This observation prompted us to further investigate this reaction system. Herein, we wish to report our preliminary studies on this subject.

Scheme 1

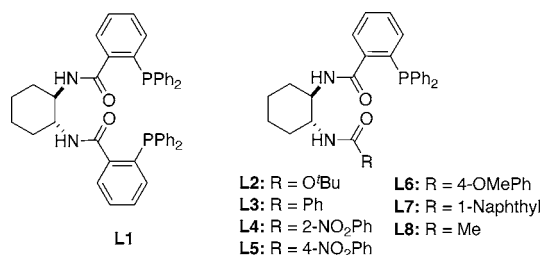
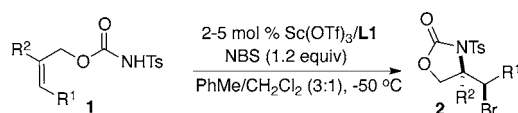
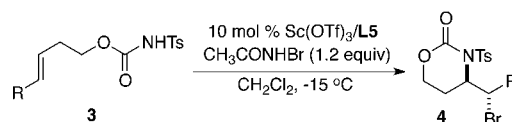


Figure 1. Selected examples of chiral ligands examined.

Scheme 2



When (*E*)-hex-3-enyl tosylcarbamate (**3b**) was first treated with *N*-bromoacetamide and 10 mol % Sc(OTf)₃-L1 complex, a messy mixture was obtained (Table 1, entry 1). It is clear that this reaction system is not effective for this class of substrates, which calls for the development of new catalysts. Various metals and ligands were subsequently examined. Ironically, high ee's were obtained with the monophosphine-Sc(OTf)₃ complex, which was previously shown to be ineffective for the asymmetric bromocyclization of (*Z*)-allyl *N*-tosylcarbamate (Scheme 1).^{10a} For example, 1,3-oxazinan-2-one **4b** was obtained in 18% yield and 93% ee with monophosphine ligand **L2** (Table 1, entry 2). Further studies showed that the yield and ee were influenced by the amide

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Table 1. Studies on the Reaction Conditions^a

entry	Br source	L	t (°C)	yield (%) ^b	ee (%) ^c
1	CH ₃ CONHBr	L1	0	messy	—
2	CH ₃ CONHBr	L2	0	18	93
3	CH ₃ CONHBr	L3	0	39	97
4	CH ₃ CONHBr	L4	0	16	92
5	CH ₃ CONHBr	L5	0	63	99
6	CH ₃ CONHBr	L6	0	58	98
7	CH ₃ CONHBr	L7	0	43	97
8	CH ₃ CONHBr	L8	0	messy	—
9	PhCONHBr	L5	0	12	98
10	NBP	L5	0	messy	—
11	TBCO	L5	0	—	—
12	DBDMH	L5	0	24	93
13	NBS	L5	0	messy	—
14	CH ₃ CONHBr	L5	rt	39	98
15	CH ₃ CONHBr	L5	-15	66	>99
16 ^d	CH ₃ CONHBr	L5	-30	60	>99
17 ^d	CH ₃ CONHBr	L5	-50	32	>99
18 ^e	CH ₃ CONHBr	L5	-15	44	99
19 ^f	CH ₃ CONHBr	L5	-15	50	99
20 ^g	CH ₃ CONHBr	L5	-15	53	99
21	CH ₃ CONHBr	—	-15	—	—
22 ^h	CH ₃ CONHBr	L5	-15	messy	—

^aThe reactions were carried out with substrate **3b** (0.10 mmol), Br source (0.12 mmol), and Sc(OTf)₃-L (1:1) (0.010 mmol) in CH₂Cl₂ (1.0 mL) for 24 h unless otherwise stated. ^bIsolated yield. ^cDetermined by chiral HPLC analysis. ^dFor 96 h. ^eWith 3 Å MS (0.025 g). ^fWith 4 Å MS (0.025 g). ^gWith 5 Å MS (0.025 g). ^hWithout Sc(OTf)₃.

substituents (Table 1, entries 2–8) with ligand L5 being the best, giving **4b** in 63% yield and 99% ee in CH₂Cl₂ at 0 °C. Among the bromine sources examined (Table 1, entries 5, 9–13), *N*-Bromoacetamide was found to be the most effective for the reaction. The reaction temperature was further examined (Table 1, entries 5, 14–17), and the optimal results were obtained at -15 °C. Lower yields were obtained when the reaction was carried out in the presence of molecular sieves (Table 1, entries 18–20). Control experiments showed that both Sc(OTf)₃ and the ligand were crucial for the reaction. Little reaction was observed with Sc(OTf)₃ alone (Table 1, entry 21), and a messy mixture was formed with ligand L5 in the absence of Sc(OTf)₃ (Table 1, entry 22).

As shown in Table 2, the bromocyclization with the Sc(OTf)₃-L5 complex can be extended to a variety of (*E*)-homoallylic *N*-tosylcarbamates (Table 2, entries 1–9) (the X-ray structure of **4b** is shown in Figure 2). While the yield was moderate, the enantioselectivity was remarkably high (97–99% ee). Various functional groups such as OBn, Cl, N₃, alkene, and alkyne can be present in the side chains (Table 2, entries 5–9). The starting material largely remained when (*E*)-4-phenylbut-3-enyl tosylcarbamate was used as the substrate (R = Ph). For (*E*)-hexa-3,5-dienyl tosylcarbamate (R = vinyl), a messy mixture was obtained. Lower ee's were obtained for (*Z*)- and terminal substrates (Table 2, entries 10 and 11).

Table 2. Enantioselective Bromoaminocyclization of Homoallylic *N*-Tosylcarbamates^a

entry	substrate	product ^c	yield (%) ^d	ee (%) ^e
1	3a ; R = Me	4a	58	99
2	3b ; R = Et	4b	57	> 99
3	3c ; R = C ₅ H ₁₁	4c	57	> 99
4	3d ; R = CH ₂ Cy	4d	54	99
5	3e ; X = OBn	4e	48	97
6 ^b	3f ; X = Cl	4f	45	99
7 ^b	3g ; X = N ₃	4g	48	98
8	3h	4h	52	> 99
9	3i	4i	59	98
10	3j	4j	57	48
11	3k	4k	72	64

^aThe reactions were carried out with substrate **3** (0.50 mmol), Sc(OTf)₃-L5 (1:1) (0.050 mmol), and CH₃CONHBr (0.60 mmol) in CH₂Cl₂ (5.0 mL) at -15 °C for 48 h unless otherwise stated. ^bThe reactions were carried out with DBDMH at 0 °C. ^cThe absolute configurations of **4b** and **4f** were assigned based on their X-ray structures. For entries 1, 3–5, and 7–9, the absolute configurations were tentatively proposed by analogy. ^dIsolated yield. ^eDetermined by chiral HPLC analysis.

The reaction can be carried out on a relatively large scale. As exemplified by **3b** (Scheme 3), 2.11 g of oxazinanone **4b**

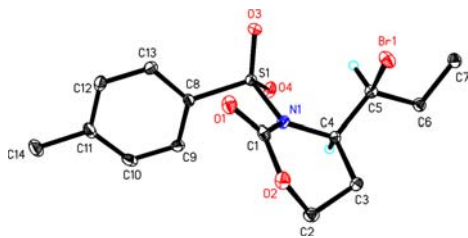
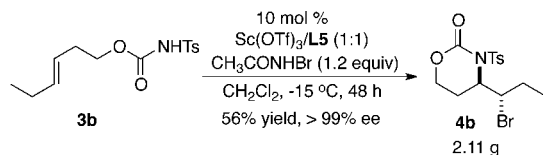


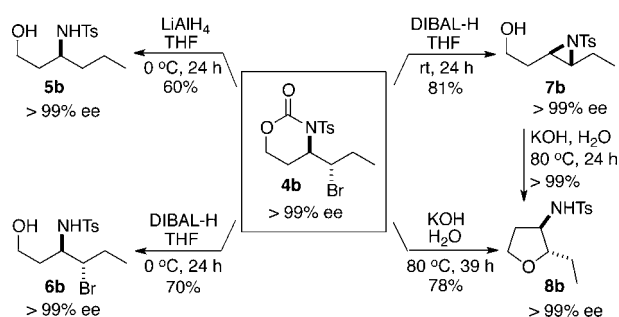
Figure 2. X-ray structure of **4b**.

Scheme 3. Bromoaminocyclization on a Gram Scale



was obtained in 56% yield with >99% ee. 1,3-Oxazinan-2-one **4b** can serve as a versatile chiral building block for further transformations as illustrated in Scheme 4. Treating **4b** with

Scheme 4. Synthetic Transformations of Bromide **4b**



LiAlH_4 at 0 °C gave aminoalcohol **5b** in 60% yield. Bromoaminoalcohol **6b** was obtained in 70% yield with DIBAL-H at 0 °C. When the reaction was carried out at rt, aziridine **7b** was formed in 81% yield. The aziridine likely resulted from the cyclization of **6b** under the reaction conditions. When **4b** was reacted with $\text{KOH-H}_2\text{O}$ at 80 °C, aminotetrahydrofuran **8b** was generated in 78% yield. Compound **8b** was formed from **4b** likely via aziridine **7b**. In all these transformations, no loss of optical purity was observed.

The different catalytic properties of $\text{Sc}(\text{OTf})_3\text{-L1}$ and $\text{Sc}(\text{OTf})_3\text{-L5}$ displayed in the bromocyclization of (*Z*)-allyl *N*-tosylcarbamates (**1**) and (*E*)-homoallylic *N*-tosylcarbamates (**3**) were intriguing. Attempts to elucidate the catalytic species involved in these reactions via NMR, MS, and X-ray spectroscopy were unsuccessful thus far. A better understanding of the reaction mechanism awaits further study.

In summary, we have developed a highly enantioselective 6-*exo*-bromoaminocyclization of (*E*)-homoallylic *N*-tosylcarbamates using *N*-bromoacetamide as the bromonium ion source and a novel chiral monophosphine- $\text{Sc}(\text{OTf})_3$ complex as the catalyst, giving the corresponding 1,3-oxazinan-2-ones in up to >99% ee. The reaction is amenable to gram scale. The resulting optically active 1,3-oxazinan-2-ones can be further transformed into various useful functionalized compounds without loss of optical purity. It appears that a delicate combination of the catalyst system and the olefin substrate

could bring opportunities to develop new reaction processes. Further efforts will be devoted to understanding the reaction mechanism, developing new catalytic systems, and expanding the substrate scope.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterizations, X-ray structures, data for determination of enantiomeric excess, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01779.

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Notes

The authors declare no competing financial interest.

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